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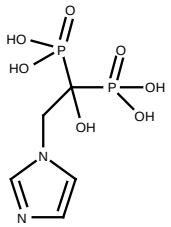
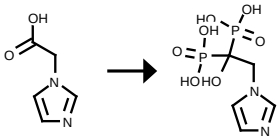
1. Query	 Search as: Product, As drawn, No salts, No mixtures	29 reactions	2011-11-16 04h:47m:48s (EST)



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Yield	Conditions & References
99 %	Example Name 7 Example 7Preparation of Zoledronic Acid; In a mixture of 20 ml of propylene carbonate and 15 ml of PEG 600 was dissolved 7.44 g of phosphorous acid at 40.deg. C. 2-(1H-imidazol-1-yl)acetic acid (3.0 g) was added while stirring and the reaction mixture was heated to 40.deg. C. To the resulting solution was added 9 ml of phosphorus trichloride. The reaction mixture was heated to 60.deg. C. and stirred at 55-60.deg. C. for 4 hours.Water (40 ml) was gradually added to the reaction mixture under stirring (hydrogen chloride is liberated). The reaction mixture was stirred at 85.deg. C. for 18 hours, cooled down to 0.deg. C. and the product was precipitated by addition of ethanol (150 ml). The precipitate was filtered off, washed with ethanol (1.x.40 ml) and dried at 60.deg. C. for 10 hours to give 6.85 g (99percent) of zoledronic acid monohydrate. **Stage 1: With** phosphoric acid, phosphorus trichoride **in** 4-methyl-1,3-dioxolan-2-one, PEG 600 (polyethylene glycol), T= 40 - 60 °C **Stage 2: With** water **in** 4-methyl-1,3-dioxolan-2-one, PEG 600 (polyethylene glycol), Time= 18h, T= 85 °C , Product distribution / selectivity **Patent**; **Kas, Martin; Benes, Michal; Pis, Jaroslav**; US2010/130746; (2010); (A1) English View in Reaxys
99 %	Example Name 7 Example Title Preparation of zoledronic acid. In a mixture of 20 ml of propylene carbonate and 15 ml of PEG 600 was dissolved 7.44 g of phosphorous acid at 40.deg.C. 2-(1H-imidazol-1-yl)acetic acid (3.0 g) was added while stirring and the reaction mixture was heated to 40.deg.C. To the resulting solution was added 9 ml of phosphorus trichloride. The reaction mixture was heated to 60.deg.C and stirred at 55-60.deg.C for 4 hours. Water (40 ml) was gradually added to the reaction mixture under stirring (hydrogen chloride is liberated). The reaction mixture was stirred at 85.deg.C for 18 hours, cooled down to 0.deg.C and the product was precipitated by addition of ethanol (150 ml).The precipitate was filtered off, washed with ethanol (1 x 40 ml) and dried at 60.deg.C for 10 hours to give 6.85 g (99percent) of zoledronic acid monohydrate. **Stage 1: With** anhydrous phosphorous acid, phosphorus trichoride **in** 4-methyl-1,3-dioxolan-2-one, PEG 600, T= 40 - 60 °C **Stage 2: With** water **in** 4-methyl-1,3-dioxolan-2-one, PEG 600, Time= 18h, T= 85 °C , Product distribution / selectivity **Patent**; **Synthon B.V.**; EP2192126; (2010); (A1) English View in Reaxys
85.6 %	Example Name 4 A mixture of 1-imidazolylacetic acid (25g; 0.1538mol) and H_3PO_3 (18.9g; 0.2306mol) in N,N'-dimethylethyleneurea (DMEU) (150ml) is heated to a temperature of from 40^0C to 50^0C. PCl_3 (26ml; 0.3076mol) is slowly added to the resulting suspension. The resulting mixture is heated to a temperature of from 50^0C to 60^0C and stirred until reaction is complete by HPLC. Water is slowly added to the reaction mixture and the resulting solution is heated, with stirring, to a temperature of from 80^0C to 100^0C until the reaction is complete. The reaction mixture is cooled to ambient temperature and the pH is adjusted to pH 8.0 to 9.0 with aqueous sodium hydroxide solution. The resulting solution is filtered and the pH of the solution is adjusted to pH 1.5 to 2.0. Ethanol is added and precipitation of solids occurs. The solid is filtered, washed and dried under vacuum at a temperature of from 45.deg.C to 55^0C to a constant weight. 25.7g of zoledronic acid is obtained (molar yield: 85.6percent) with a HPLC purity higher than 99.5percent in area. [The yield was calculated on dry basis]The product was characterized as follows:^{1}H NMR (D_2O) δ=4.71 (t, 2H, CH_2); 7.28 (dd., IH_3CH); 7.44 (dd., IH, CH); 8.62 (s., IH, CH)^{31}P NMR (D_2O) δ= 16.03 **Stage 1: With** anhydrous phosphorous acid, phosphorus trichoride **in** N,N'- dimethylethyleneurea (DMEU), T= 40 - 60 °C **Stage 2: With** water **in** N,N'- dimethylethyleneurea (DMEU), T= 80 - 100 °C **Patent**; **HOVIONE INTER LIMITED; TURNER, Craig, Robert**; WO2008/56129; (2008); (A1) English

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83 %	Example Name 1 Example 1 - Zoledronic Acid; EPO <DP n="7"/>A suspension of 1-imidazol-l-yl acetic acid (200 g) in methanesulfonic acid 98-99 percent (240 ml) is added slowly and blending phosphorous trichloride (856 ml).The temperature is increased until reaching 55 ^{0}C, reflux is observed.Once the phosphorous trichloride aggregate is finished, the aggregate of water (171 ml) is started, thus increasing the exothermy, which is evidenced through a larger volume of reflux.During the reaction hydrogen chloride is released.The mass in suspension slowly dissolves and the solution turns very viscous, thus making the agitation difficult.After 12 hours reaction at 55-70 ^{0}C, water is slowly added (805 ml), in a period of 2-3 hours at a temperature between 8 and 25 ^{0}C, with which a fluid solution is achieved.It is then heated at 105 - 112 ^{0}C over 3 hours and the solution is filtered to eliminate impurities.The resulting solution is partially neutralized at a temperature of 30 - 40 ^{0}C with a sodium hydroxide aqueous solution 50 percent (w/v) until obtaining a pH of 0.25 +/- 0.03It is then cooled down to 0-5 ^{0}C, maintaining this temperature over at least 2 hours the precipitate being filtered.The same is washed by resuspension once in water (500 ml) and twice in methanol (500 ml each time).The precipitate may be dried in a stove at 50 - 60 ^{0}C, thus obtaining the raw zoledronic acid with a potentiometric titre equal to or exceeding 98 percent.It may also be used humid to prepare the trihydrate form.The output is 83 percent. **Stage 1: With** methanesulfonic acid, phosphorus trichoride, T= 55 °C **Stage 2: With** water, Time= 14 - 15h, T= 8 - 70 °C **Stage 3: With** sodium hydroxide **in** water, T= 30 - 40 °C , pH= 0.25 **Patent**; **GADOR S.A.**; WO2007/16982; (2007); (A1) English View in Reaxys
80 %	**Stage 1: With** p-cresol, phosphoric acid, phosphorus trichoride, Time= 8h, Heating **Stage 2: With** water, Heating, Further stages. **Rao, Divvela V. N. Srinivasa; Dandala, Ramesh; Narayanan, Garimella K. A. S. S.; Lenin, Racha; Sivakumaran, M.; Naidu, Andra**; Synthetic Communications; **vol.** 37; nb. 24; (2007); p. 4359 - 4365 View in Reaxys
75 %	Example Name 2 The suspension of (1-imidazoyl)ethanoic acid (10.0 g) and phosphorous acid (19.5 g) in diphenyl ether (50 ml) was heated up to 70.deg. C. for 1 hour. Phosphorous trichloride (20 ml) was slowly added to reaction mass at 70.deg. C. temperature and maintained reaction temperature for another 6 hours. Reaction mass was cooled to 25.deg. C. followed by addition of water (150 ml) and toluene (30 ml). Reaction mixture was again heated to 70.deg. C. and charged charcoal in hazy biphasic solution, stirred, filtered through Hyflo bed, washed the bed with hot water (30 ml). Layers was separated from filtrate, aqueous layer was washed with toluene (20 ml) and combined organic layer was then back extracted with water (20 ml) and mixed with main aqueous layer. The water (140 ml) was distilled out from combined aqueous layer at atmospheric pressure in 2 hours and then refluxed the concentrated mass for 13 hours. Reaction mass was cooled to 25.deg. C. followed by addition of methanol (50 ml) in 1 hours. The reaction mixture was stirred and again cooled to 0.deg. C. followed filtration. The filtrate was washed with chilled 1:2 mixture (30 ml) of water and methanol and dried at 60.deg. C. to get Zoledronic Acid. Yield: 19.0 gm (75percent) **Stage 1: With** anhydrous phosphorous acid **in** diphenylether, Time= 1h, T= 70 °C **Stage 2: With** phosphorus trichoride **in** diphenylether, Time= 6h, T= 70 °C **Stage 3: With** water **in** diphenylether, toluene, T= 25 °C **Patent**; **ALEMBIC LIMITED**; US2006/258625; (2006); (A1) English View in Reaxys
72 %	Example Name 8 Examples; CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac); Preparation of ZLD-AC crystal form I; General procedure for the preparation of ZLD-AC crystal form I starting from 1- Imidazoleacetic acid (IAA), Phosphorous acid (H3PO3) and Phosphorous oxychloride (POC13) (Examples 1-9, see Table 1) :; A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-IMIDAZOLEACETIC acid (IAA), Phosphorous acid and a diluent (Toluene/Chlorobenzene/PEG-400/Silicon oil). The obtained suspension is heated to 75.deg.C-80.deg.C and Phosphorous oxychloride is added drop- wise. The reaction mixture is then heated to 75.deg.C-100.deg.C for 1-34 hours. Then water is added at 80.deg.C-100.deg.C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95.deg.C-100.deg.C for 13.5-19 hours. Then it is cooled to 5.deg.C and absolute Ethanol is added to obtain a precipitate after stirring at 5.deg.C for 2.5-4 hours [In some cases a precipitate

	of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50.deg.C for 17-24 hours to obtain Zoledronic acid crystal form I (LOD BY TGA=6. 3percent-9. 3percent).; ZLD HPLC METHOD: COLUMN: PHENOMENEX PHENYL-HEXYL 5UM, 250X4.6MM MOBILE PHASE: 40MM OCTANSULFONIC ACID SODIUM SALT IN 1percent HCLO4, 0.2percent H3PO4 : METHANOL (85:15) DETECTION: 220NM STABILITY WAS MEASURED VERSUS THE PRESENCE OF FORM II. P THE STABILITY DATA FOR EXAMPLE 4 IN THE TABLE ABOVE IS: **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** silicon oil, Time= 17h, T= 80 °C **Stage 2: With** water **in** silicon oil, Time= 16h, T= 80 - 100 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
70.7 %	Example Name 6 Preparation of zoledronic acid monohydrate A suspension of 1-imidazolylacetic acid (50g, 0. 396mol) and phosphorous acid (48.7g, 0. 594mol) in sulfolan (180ml) is heated to 75.deg.C for 30 min. The mixture is cooled to 35-40.deg. C and then gradually introduced phosphorous trichloride (117ml, 1. 346mol) while maintaining the temperature between 35-45.deg.C. The mixture is heated to 63-67.deg.C for 3hrs, whereby white solid results. It is then cooled to 0-5.deg.C and quenched by slow addition of water (500ml) at 0-5.deg.C over a period of 1 hr. The resulting clear solution is heated at 100.deg.C for 3hrs, cooled to ambient temperature and charcoalized. To the charcoalized solution is added acetone (800ml). The mixture is then stirred for 4hrs at 20- 25.deg.C and the crystallized product is filtered, washed sequentially with chilled water (200ml), acetone (100ml) and dried in air oven at 55-60.deg.C until water content is between. **Stage 1: With** anhydrous phosphorous acid **in** sulfolane, Time= 0.5h, T= 75 °C **Stage 2: With** phosphorus trichoride **in** sulfolane, Time= 3h, T= 35 - 67 °C **Stage 3: With** water **in** sulfolane, Time= 8h, T= 0 - 100 °C **Patent**; **SUN PHARMACEUTICAL INDUSTRIES LIMITED**; WO2005/44831; (2005); (A2) English View in Reaxys
70 %	Example Title General procedure for the microwave synthesis of nitrogen-containing 1-hydroxyl BPs 3.8 mmol (1 equiv) of the respective carboxylic acid (658 mg 3-pyridylacetic acid hydrochloride for 1, 478 mg imidazol-1-yl-acetic acid for 2, 339 mg β-alanine for 3, 392 mg γ-aminobutyric acid for 4, 499 mg 6-aminohexanoic acid for 5) were added to 11.4 mmol (3 equiv) H_3PO_3 in a dry flask. 1.6 mL of distilled sulfolane was added and the contents were heated briefly to dissolve the solids. The solution was cooled down to approximately 25-35 .deg.C, and 11.4 mmol (3 equiv) of PCl_3 were immediately added. The flask was then placed in a Milestone Ethos Synth Microwave Synthesis Labstation and fitted with a condenser through which cold water was passed. The following microwave programs were applied:For synthesis of 1: 3 min ramp to 65 .deg.C, followed by 15 s at 65 .deg.C. For synthesis of 2: 3 min ramp to 65 .deg.C, followed by 45 s at 65 .deg.C.For synthesis of 3: 3 min ramp to 65 .deg.C, followed by 15 s at 65 .deg.C.For synthesis of 4: 3 min ramp to 65 .deg.C, followed by 4 min at 65 .deg.C.For synthesis of 5: 3 min ramp to 65 .deg.C, followed by 4 min at 65 .deg.C.The power was automatically adjusted to reach and maintain the temperature designated by the program, which is determined by a built-in IR sensor in the microwave reactor. For the synthesis of intermediates 1 and 2, the power fluctuated between 0 and a max of 300-400 W, while for 3, 4, and 5, the max power was typically 200-300 W.The solid mixture after microwave irradiation consists of intermediate phosphorus compound together with a yellow-orange unwanted side product which can be removed by centrifugation before or after hydrolysis. The reaction mixture was quenched with 6 mL of H_2O, yielding a clear solution that was then transferred to a 50 mL sealed quartz reaction vessel and was hydrolyzed to the bisphosphonic acid in the microwave reactor with a 6 min ramp to 150 .deg.C, followed by 4 min at 150 .deg.C. The power applied fluctuated between 0 and a max of 450-500 W. The pH of the hydrolysis mixtures for acids 1, 3, 4, and 5 was adjusted[15] with NaOH and the mixture then aged at 0-5 .deg.C until crystallization of the products was complete. Acids 4 and 5 were precipitated as monosodium salts by stirring with 2-5 mL ethanol for 1-2 h at room temperature. Acid 2 was precipitated by the addition of 9 mL acetone to the acidic hydrolysis mixture and stirring for 3-4 h at room temperature. The white crystalline products were then filtered and washed with cold H_2O and acetone or ethanol and then dried under vacuum at 45 .deg.C to constant weight.[15] with NaOH and the mixture then aged at 0-5 .deg.C until crystallization of the products was complete. Acids 4 and 5 were precipitated as monosodium salts by stirring with 2-5 mL ethanol for 1-2 h at room temperature. Acid 2 was precipitated by the addition of 9 mL acetone to the acidic hydrolysis mixture and stirring for 3-4 h at room temperature. The white crystalline products were then filtered and washed with cold H_2O and acetone or ethanol and then dried under vacuum at 45 .deg.C to constant weight. **Stage 1: With** orthophosphorus acid, phosphorus trichoride **in** sulfolane, Time= 0.0625h, T= 25 - 65 °C , Microwave irradiation

	Stage 2: With water **in** sulfolane, Time= 0.166667h, T= 150 °C , Microwave irradiation **Mustafa, Dana A.; Kashemirov, Boris A.; McKenna, Charles E.**; Tetrahedron Letters; **vol.** 52; nb. 18; (2011); p. 2285 - 2287 View in Reaxys
67 %	**With** phosphoric acid, phosphorus trichoride **in** chlorobenzene, Time= 3h, T= 100 - 110 °C **Widler, Leo; Jaeggi, Knut A.; Glatt, Markus; Mueller, Klaus; Bachmann, Rolf; Bisping, Michael; Born, Anne-Ruth; Cortesi, Reto; Guiglia, Gabriela; Jeker, Heidi; Klein, Remy; et al.**; Journal of Medicinal Chemistry; **vol.** 45; nb. 17; (2002); p. 3721 - 3738 View in Reaxys
59 %	Example Name 9 Examples; CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac); Preparation of ZLD-AC crystal form I; General procedure for the preparation of ZLD-AC crystal form I starting from 1- Imidazoleacetic acid (IAA), Phosphorous acid (H3PO3) and Phosphorous oxychloride (POC13) (Examples 1-9, see Table 1) :; A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-IMIDAZOLEACETIC acid (IAA), Phosphorous acid and a diluent (Toluene/Chlorobenzene/PEG-400/Silicon oil). The obtained suspension is heated to 75.deg.C-80.deg.C and Phosphorous oxychloride is added drop- wise. The reaction mixture is then heated to 75.deg.C-100.deg.C for 1-34 hours. Then water is added at 80.deg.C-100.deg.C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95.deg.C-100.deg.C for 13.5-19 hours. Then it is cooled to 5.deg.C and absolute Ethanol is added to obtain a precipitate after stirring at 5.deg.C for 2.5-4 hours [In some cases a precipitate of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50.deg.C for 17-24 hours to obtain Zoledronic acid crystal form I (LOD BY TGA=6. 3percent-9. 3percent).; ZLD HPLC METHOD: COLUMN: PHENOMENEX PHENYL-HEXYL 5UM, 250X4.6MM MOBILE PHASE: 40MM OCTANSULFONIC ACID SODIUM SALT IN 1percent HCLO4, 0.2percent H3PO4 : METHANOL (85:15) DETECTION: 220NM STABILITY WAS MEASURED VERSUS THE PRESENCE OF FORM II. P THE STABILITY DATA FOR EXAMPLE 4 IN THE TABLE ABOVE IS: **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** silicon oil, Time= 34h, T= 80 °C **Stage 2: With** water **in** toluene, silicon oil, Time= 16h, T= 80 - 100 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
53 - 65 %	Example Name 1; 2; 3; 4 Example 1; [0022] An oven-dried 250 ml_ 4-neck RB flask was fitted with a mechanic stirrer, K-thermocouple, condenser, nitrogen inlet and outlet and two 1/8 inch polytetrafluoroethylene (PTFE) feeding lines. The system was flushed with nitrogen for 30 minutes. Under nitrogen protection, imidazole-1-ylacetic acid (15.97 g, 0.13 mole), sulfolane (70 ml_) and phosphorous acid (2.67 g, 0.033 mol) were charged to the RB flask. The reaction mixture was mixed at 210 RPM and heated to 60^0C. PCl_3 (9.18 g, 0.067mol) was added slowly (1.3 mL/mn) via a masterflex tubing pump. Five minutes were allowed for mixing. Alternately fed were 26 wtpercent phosphorous acid sulfolane solution (30.7 g, 10.23 g each addition at 1.6 mL/min) and PCl_3 (27.5 g, 9.18 g each portion at 1.3 mL/min). Three to five minutes of mixing were allowed between additions. The addition took 1 hr 3 min and temperature was maintained between 60^0C and 67^0C. After addition was complete, the temperature of the reaction mixture was raised to 80^0C and was held at this temperature for 4 hours. Then the temperature of the reaction mixture was raised to 88^0C and held for 30 minutes. Ambient temperature water (50 g) was added in to quench the reaction. The solution was refluxed for 3 hrs <n="13"/>. temperature, the product was vacuum-filtered and rinsed with 38 g of acetone. Zoledronic acid was obtained as a white crystalline solid (24.1 g, 95.3wtpercent purity by quantitative NMR, 65percent yield). Example 2; [0023] An oven-dried 250 mL 4-neck RB flask was fitted with a mechanic stirrer, K-thermocouple, condenser, nitrogen inlet and outlet and two 1/8 inch PTFE feeding lines. The system was flushed with nitrogen for 30 minutes. Under nitrogen protection, imidazole-1-ylacetic acid (15.97 g, 0.13 mole), sulfolane (70 mL) and phosphorous acid (2.67 g, 0.033 mol) were charged to the RB flask. The reaction mixture was mixed at 300 RPM and heated to 60^0C. PCl_3 (9.18 g, 0.067mol) was added in slowly (1.3 mL/min) via a masterflex tubing pump. Five minutes were allowed for mixing. Alternately fed were 26 wtpercent phosphorous acid sulfolane solution (30.7 g, 10.23 g each addition at 1.6 mL/min) and PCl_3 (27.5 g, 9.18 g each portion at 1.3 mL/min. Three to five minutes of mixing were allowed between additions. The addition took 1 hr 6 min and temperature was maintained between 54 and 64.deg.C. After addition was complete, the temperature of the reaction mixture was raised to 80^0C and held for 4 hours. Then the temperature of the reaction mixture was raised to

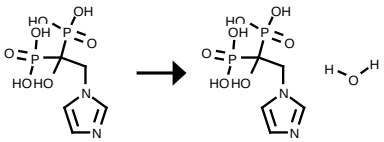
	88^{0}C and held for 30 minutes. This slurry was transferred via 3/8" PTFE tubing using nitrogen pressure into 100 mL of pre-heated (80.deg.C) water under mixing. The resultant water solution was heated to refluxing and held at that temperature for 4 hr. It was then slowly cooled to room temperature then to 1-2.deg.C and held for 1.5 hr at this temperature. The product was collected via vacuum filtration. The cake was rinsed with acetone (20 g) and zoledronic acid was obtained as a white crystalline solid (19.1 g, 98.3 wtpercent purity by quantitative NMR, 53percent yield). Example 3; [0024] An oven-dried 250 mL 4-neck RB flask was fitted with a mechanic stirrer, K-thermocouple, condenser, nitrogen inlet and outlet and two 1/8 inch PTFE feeding lines. The system was flushed with nitrogen for 30 minutes. Under nitrogen protection, imidazole-1-ylacetic acid (15.9 g, 0.13 mole), sulfolane (70 mL) and phosphorous acid (2.67 g, 0.033 mol) were charged to the RB flask. The reaction mixture was mixed and heated to 6O^{0}C. PCl_3 (36.7 g, 0.267 mol) and phosphorous acid (8.0 g, 0.098 mol) in <n="14"/>- . mL/min respectively. Reaction temperature remained between 6O^{0}C and 67.deg.C during feeding, After addition of PCl_3 and phosphorous acid, the reaction slurry was heated to 80^{0}C and held at that temperature for 4 hours. This slurry was then transferred via 3/8" PTFE tubing using nitrogen pressure into 50 m._ of pre-heated (8O^{0}C) water under mixing. The resultant water solution was heated to refluxing and held at that temperature for 4 hr. It was then slowly cooled to 48-50^{0}C. Acetone (200 ml_) was added in slowly and then it was cooled to 1-2.deg.C and held for 2 hr at this temperature. The product was collected via vacuum filtration. The cake was rinsed with acetone (35 g) and zoledronic acid was obtained as a white crystalline solid (22.1 g, 98.6 wtpercent purity by quantitative NMR, 61 percent yield). Example 4; [0025] A 2.5 L resin-kettle was fitted with a mechanic stirrer, K-thermocouple, condenser, nitrogen inlet and outlet, two 1/8 inch PTFE tubing as PCl_3 and phosphorous acid sulfolane solution feeding lines. The system was dried under a stream of nitrogen. Under nitrogen, imidazoleacetic acid (79.92 g, 0.63 mol), phosphorous acid (13.90 g, 0.17 mol) and sulfolane (350 ml_) were added to the resin-kettle and mixed at 200 RPM. The mixture was heated to 62.deg.C then PCl_3 (36.7 g, 0.267 mol) was added in slowly (1.3 mL/min) using a masterflex tubing pump. The slurry was mixed for 5 minutes. Phosphorous acid (40.0 g, 0.49 mol) was dissolved in 114.0 g of sulfolane at 50^{0}C. Alternately, this solution (30.8 g each time at 1.6 mL/min) and 147 g (1.07 mol) of PCl_3 (29.5 g each portion at 1.3 mL/min) were fed into the reactor while the reaction temperature was maintained at 60-64^{0}C. Three to five minutes mixing time was allowed between each addition. Toward the second half of the alternate addition, addition rates were increased to 2.0 mL/min for PCl_3 and 2.5 mL/min for phosphorous acid solution respectively. The addition took 3 hr and 21 minutes. After the addition was complete, the phosphorous acid line was rinsed with 30 mL of sulfolane and this was added into the resin-kettle reactor. The reaction temperature was then raised to 80^{0}C and maintained for 4 hours. The resulting slurry was then quenched into 250 g of water pre-heated to 80^{0}C under mixing. The aqueous solution was refluxed for 4 hours and cooled slowly to room temperature resulting in a slurry. Acetone (1 L) was added slowly into the slurry and the mixture was cooled further to 1-2 ^{0}C. After mixing for 2 hours at this temperature, the product was vacuum <n="15"/>, hour. Zoledronic acid was obtained as a white, crystalline solid (109.6 g). **Stage 1: With** phosphoric acid, phosphorus trichoride **in** sulfolane, Time= 5.55 - 7.35h, T= 54 - 88 °C **Stage 2: With** water **in** sulfolane, Time= 3 - 4h, Heating / reflux, Product distribution / selectivity **Patent**; **ALBEMARLE CORPORATION**; WO2008/157050; (2008); (A1) English View in Reaxys
53 %	Example Title Preparation of [1-hydroxy-2-(1H-imidazol-1-yl)-ethylidene]bisphosphonic acid (ZA): 6.3 g (0.05 mol) of imidazol-1-yl-acetic acid was dissolved in 21 ml of methanesulfonic acid with stirring. 13.6 ml (0.16 mol) of phosphorus trichloride was added dropwise and the mixture was stirred at 80 .deg.C for 3 h. After cooling to 26 .deg.C, 36 ml of water was added dropwise, the temperature was elevated to 105-110 .deg.C and the contents of the flask were stirred at this temperature for 5 h. Next, the mixture was stirred with 0.75 g of activated carbon for 30 min, filtered and the solid washed with 5 ml of water. To the combined water phase was added dropwise 10 N NaOH solution to attain pH 1.8. The suspension obtained was stirred for 5 h, the solid filtered, washed with 5 ml of water and dried to afford 9.7 g (71percent) of a crude mixture consisting of a 26-74percent mixture of ZA and ZA-Na. Recrystallization from 48.5 ml of 1 N hydrochloric acid furnished 7.2 g (53percent) of ZA comprising 99percent of the acid (Table 1, entry 7); ^{31}P NMR (5percent NaOH/D2O) 16.0 [P^8 (5percent NaOD/D2O) 16.2]. **Stage 1: With** phosphorus trichoride **in** methanesulfonic acid, Time= 3h, T= 80 °C **Stage 2: With** water **in** methanesulfonic acid, Time= 5h, T= 26 - 110 °C **Stage 3: With** sodium hydroxide **in** water, Time= 5h, pH= 1.8 **Keglevich, Gyoergy; Gruen, Alajos; Aradi, Klara; Garadnay, Sandor; Greiner, Istvan**; Tetrahedron Letters; **vol.** 52; nb. 21; (2011); p. 2744 - 2746 View in Reaxys
50 %	Example Name 18

	PREPARALION OF ZLD-AC CRYSTAL FORM XNII; Example 18 :; A 3L reactor equipped with A mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with 1-IMIDAZOLEACETIC acid (70. OG, 0. 56MOLE), Phosphorous acid (136. 7g, 1.67mole) and Silicon oil (M-350) (490ML). The suspension was heated to 80.deg.C and Phosphorous oxychloride (194. 4ML, 2.08mole) was added drop-wise during 4 hours. The reaction mixture was stirred at 80.deg.C for 22 hours. Then water (490ML) was added slowly at 80.deg.C. The mixture was stirred vigorously for about 30 minutes. Then the silicon oil phase and the aqueous phase were separated. The aqueous phase was put in a clean reactor and heated to 97.deg.C for 17.5 hours. Then absolute Ethanol (490ML) was added and the solution was stirred at reflux (87.deg.C) for 2 hours. The solution was then cooled to 70.deg.C-72.deg.C during about 1 hour and was kept at this temperature for 1 hour. After cooling to 25.deg.C during 2.5 hours and stirring at this temperature for 1 hour, half of the product was filtered, washed with small amount of cold water and dried in a vacuum oven at 50.deg.C for 20 hours to obtain 50.8g of Zoledronic acid crystal form XVIII (MS- 507-CROP I, LOD by TGA=1.9percent). The rest of the suspension was cooled to 0.deg.C during 2 hours and was stirred at this temperature for about 16 hours. Then the product was filtered and dried in a vacuum oven at 50.deg.C for 24 hours to obtain 26g of Zoledronic acid crystal form XVIII (MS-507-CROP II, LOD by TGA=1. 0percent). The overall yield of the process is 50percent purity by HPLC 97.7percent. **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** silicon oil, Time= 26h, T= 80 °C **Stage 2: With** water **in** ethanol, silicon oil, Time= 43.5h, T= 0 - 97 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
49 %	Example Name II Example II. Preparation of [l-hydroxy-2-(lH-imidazol-l-yl)- ethylidene]bisphosphonic acid.A solution of lH-imidazole-1 - acetic acid [26 g (0.206 moles) of lH-imidazole-1- acetic acid in the mixture of 18 ml of water and 18 ml of hydrochloric acid (35percent)] is added dropwise for 30 minutes at the temperature 0-5 ^{0}C to 108 ml of phosphorus trichloride (PCl_3) cooled to the temperature 0-5 ^{0}C. The mixture is mixed at 0-5^{0}C for 1 hour. Then, the mixture is heated to 80^{0}C and maintained at this temperature for 1 hour. The excess of phosphorus trichloride is then distilled off under the reduced pressure. 200 ml of water is added to the reaction residues and the hydrolysis is performed while maintaining boiling for 6 hours, afterwards 1 g of activated charcoal, 5 g of Hyflo Super Cel are added and mixed while boiling for 30 minutes. The mixture is filtered and the filter is washed with 20 ml of water. The filtrate is concentrated under the reduced pressure to the volume of 100 ml. 150 ml of 95percent ethanol is added to the concentrated filtrate at 70.deg.C. The mixture is cooled while mixing to 25^{0}C and crystallization is performed until the temperature reaches 20-25^{0}C for 4 hours. The formed precipitate is filtered off, washed twice with 30 ml of water-ethanol mixture (1:1.5) and dried at 5O^{0}C. 29.3 g (49percent) of [l-hydroxy-2-(lH-imidazol-l-yl)-ethylidene]bisphosphonic acid monohydrate is obtained. HPLC 100.00percent , TGA 6.30percentXPRD: 12.05; 12.77; 15.69; 18.80; 20.84; 21.25; 21.71; 22.09; 25.71; 27.50; 29.19; 32.42; 32.88 .deg. (+,- 0,02 .deg.) 2 ψ^{1}H NMR (D_2O): 5=4.670-4.709 ppm (t, 2H, J=9.65); 7.379 (s,lH); 7.540 (s, IH);8.719 (s, IH)^{13}C NMR: 5=55.56 ppm; 74.81-76.90 (t); 121.13; 126.83; 138.71^{31}P NMR: 5=14.36 ppm15 g of [l-hydroxy-2-(l/-^{r}-imidazol-l-yl)-ethylidene]bisphosphonic acid is suspended in 300 ml of water, heated to the boiling point and mixed while boiling for 15 minutes. Then, the mixture is cooled to 70.deg.C and 300 ml of ethanol is added for about 1-1.5 hour. The mixture is cooled to 20-25.deg.C. After 14 hours of mixing in20-25.deg.C the precipitate is filtered off, washed twice with 15 ml of water and once with 15 ml of ethanol and dried for 6 hours at 55.deg.C. 12.78 g (85percent) of [l-hydroxy-2-(lH-imidazol-l-yl)-ethylidene]bisphosphonic acid monohydrate is obtained.HPLC 100.00percent, TGA 6.24percentXPRD: 12.05; 12.78; 15.72; 18.70; 20.82; 21.23; 21.70; 22.08; 25.70; 27.51; 29.14;32.32; 32.88 .deg. (+,- 0.02 .deg.) 2 ψ 1H NMR (D_2O): 5=4.470-4.497 ppm (t, 2H, J=9.62); 7.164 (s,lH); 7.367 (s, IH);8.421 (s, IH)^{13}C NMR: 5=53.00 ppm; 72.59 (t); 118.47; 123.66; 138.71^{31}P NMR: 5=14.21 ppm **Stage 1: With** hydrogenchloride, phosphorus trichoride **in** water, Time= 2.5h, T= 0 - 5 °C **Stage 2: With** water, Time= 6h, Reflux, Product distribution / selectivity **Patent**; **ZAK.pnd.ADY FARMACEUTYCZNE POLPHARMA SA; POLITECHNIKA GDANSKA; DEMBKOWSKI, Leszek; KRZYZANOWSKI, Mariusz; RYNKIEWICZ, Robert; SZRAMKA, Roman; ROZNERSKI, Zdzislaw; ZY.pnd.A, Daniel; RACHON, Janusz; MAKOWIEC, Slawomir**; WO2010/50830; (2010); (A1) English View in Reaxys
28 %	Example Name 3; 4 Example 3:Preparation of Zoledronic Acid:[0019] A 1.5 liter kettle reactor, fitted with a heating mantle, mechanical stirrer, dropping funnel, thermocouple and condenser with nitrogen inlet adapter, was charged with imidazoleacetic acid (100 g, 0.793 mol), diglyme (400 ml), and 85percent phosphoric acid (55 ml). Phosphorus trichloride (330 g, 2.41 mol) was slowly added to the reaction mass resulting in an exotherm and the evolution of hydrogen chloride. The temperature was allowed to rise to 70^{0}C and the solution was stirred until the evolution of HCl subsided. The temperature

	of the reaction mass was increased to 85.deg.C and a white solid began to form, float and adhere to the stirrer shaft. After about 1 hour, stirring became impossible and the stirring motor was stopped. The reaction mass was heated for 5 more hours at 85.deg.C and then cooled to ambient temperature, producing a solid homogeneous white mass. <n="8"/>[0020] Water was slowly added to the white mass (320 ml) that resulted in an exotherm and HCl evolution. The water slowly dissolved the mass in a gradual and uniform fashion, eventually liberating the stirrer. After the mass substantially dissolved, the solution was refluxed for 5 hours, then cooled and stripped to a gum with a rotary evaporator, collecting 420 g of water (pH 0.65). More water (250 ml) was added and stripped, collecting 166 g of water (pH 1.87). Water (250 ml) was again added and stripped, collecting 316 g (pH 2.14). The flask was removed from the rotary evaporator, water (150 ml) was added and the mixture was heated to 90-95^{0}C during which time all solids dissolved. The solution was seeded with zoledronic acid monohydrate crystals and slowly cooled to room temperature then chilled to 3^{0}C with an ice bath. The resulting crystalline solid was filtered, rinsed with acetone (200 + 100 ml) and dried under a nitrogen stream giving a crop of 52.4 g. Acetone was also added to the filtrate (200 ml) and the solution was left in a freezer overnight giving a second crop of crystals (12.0 g) which, after washing with acetone and drying, was combined with the first crop for a total yield of 64.4 g (28percent). The NMR indicated the presence of traces of diglyme, acetone and H_3PO_3 impurities. Example 4:Preparation of Zoledronic Acid:[0021] A 5 liter cylindrical jacketed reactor was fitted with a mechanical stirrer, thermocouple, nitrogen inlet adapter and a condenser with a caustic scrubber. This was charged with imidazo-leacetic acid (0.333 kg, 2.64 mol) and diglyme (1.00 1). The slurry was heated to 50^{0}C while stirring (100 rpm) under a slow nitrogen purge (1 1/min). Additional diglyme (0.26 1) and 85percent phosphoric acid (0.304 kg) were added to the reaction mass. Using a Masterflex pump and Teflon tubing, phophorus trichloride (1.04 kg total, 7.57 mol) was pumped into the reaction mass, slowly (2 ml/min) at first and then at an increased rate (40 ml/min), after the water in the phosphoric acid had been depleted. During addition of the PCl_3, the temperature was raised to about 65.deg.C and a white mass gradually formed, causing the stirrer to bind. The jacket temperature was increased to 85^{0}C causing PCl_3 to reflux. The refluxing slowed and then stopped as the white mass expanded. The reactor was allowed to stand at about 80.deg.C for four hours, after which the jacket temperature was set at 15^{0}C overnight.[0022] The reactor jacket temperature was increased to 50^{0}C and water (0.95 kg total) was slowly (2-5 ml/min) added with a Masterflex pump. The water dissolved the white mass on contact, liberating HCl in an exothermic reaction. After about 250 g of water was added to the reaction mass, the stirrer became unbound and stirring was resumed (100 rpm). The water <n="9"/>addition rate was slowly increased to 40 ml/min. The reaction mass was then heated at about 100^{0}C for 4 hours and then cooled to room temperature.[0023] The reaction mass was drained and rotary evaporated to yield a gum. Water was added to the gum and stripped several times until the distillates pH rose above 1. The resulting aqueous solution (1.2 kg, 1.6 1) was stirred in a beaker and acetone (1.5 1) was slowly added. The mixture was allowed to stand 16 hours to complete crystallization. The solid was filtered, thoroughly washed with acetone and dried in a nitrogen stream to give crude Zoledronic acid (0.202 g, 0.74 mol, 28percent yield). **With** phosphoric acid, phosphorus trichoride **in** diethylene glycol dimethyl ether, water, Time= 8 - 11h, T= 50 - 100 °C , Heating / reflux, Product distribution / selectivity **Patent**; **ALBEMARLE CORPORATION**; WO2007/109542; (2007); (A2) English View in Reaxys
7 %	Example Name 6 Example 6:(Comparative) Preparation of Zoledronic Acid in PEG-400:[0025] Example 3 was repeated substituting PEG-400 (400ml) for diglyme. After the addition of phosphorus trichloride and increased temperature of the reaction mass, a solid formed that eventually returned to solution upon further heating. The yield of zoledronic acid was 7 percent (isolated yield). ^{1}HNMR (D_2O/NaOD): 7.72 (s, 1 H); 7.22 (s, 1 H); 6.87 (s, 1 H); 4.82 (O-H, 7.02 H); 4.45 (m, 2 H). ^{31}P NMR (D_2O/NaOD): 17.0 (m). Not only was there a substantial decrease in yield, but the product purity deteriorated as well. **With** phosphoric acid, phosphorus trichoride **in** water, PEG 400, Time= 11h, T= 70 - 85 °C , Heating / reflux, Product distribution / selectivity **Patent**; **ALBEMARLE CORPORATION**; WO2007/109542; (2007); (A2) English View in Reaxys
	Stage 1: With pyridine, hydrogenchloride, phosphorus trichoride, T= 95 °C **Stage 2: With** hydrogenchloride, T= 135 °C **Ghosh, Subhash; Chan, Julian M. W.; Lea, Christopher R.; Meints, Gary A.; Lewis, Jared C.; Tovian, Zev S.; Flessner, Ryan M.; Loftus, Timothy C.; Bruchhaus, Iris; Kendrick, Howard; Croft, Simon L.; et al.**; Journal of Medicinal Chemistry; **vol.** 47; nb. 1; (2004); p. 175 - 187 View in Reaxys

	Stage 1: With pyridine, hydrogenchloride, phosphorus trichoride **Stage 2: With** hydrogenchloride, Heating **Sanders, John M.; Gomez, Aurora Ortiz; Mao, Junhong; Meints, Gary A.; Brussel, Erin M. Van; Burzynska, Agnieszka; Kafarski, Pawel; Gonzales-Pacanowska, Dolores; Oldfield, Eric**; Journal of Medicinal Chemistry; **vol.** 46; nb. 24; (2003); p. 5171 - 5183 View in Reaxys
	Example Name 4 A suspension of imidazol-1-ylacetic acid, compound of formula 2 (50g, 0. 396mol) and phosphorous acid (48.7g, 0. 594mol) in sulfolan (180ml) was heated to 75.deg. C for 30 min. The mixture was cooled to 35-40.deg. C and phosphorous trichloride (117ml, 1. 346mol) was gradually introduced while maintaining the temperature between 35-45.deg. C. The mixture was heated to 63-67.deg. C for 3 hours, whereby white solid results. It was then cooled to 0- 5'C and quenched by slow addition of water (500ml) at 0-5.deg. C over a period of 1 hour. The resulting clear solution was heated at 100.deg. C for 3 hours, cooled to ambient temperature and charcoalized. Acetone was added to the charcoalized solution. The mixture was then stirred for 4 hours at 20-25.deg. C and the crystallized product was filtered, washed sequentially with chilled water, acetone and dried to obtain zoledronic acid. **Stage 1: With** orthophosphorus acid **in** sulfolane, Time= 0.5h, T= 75 °C **Stage 2: With** phosphorus trichoride **in** sulfolane, Time= 3h, T= 35 - 67 °C **Stage 3: With** water, Time= 4h, T= 0 - 100 °C **Patent**; **SUN PHARMACEUTICAL INDUSTRIES LIMITED**; WO2005/66188; (2005); (A1) English View in Reaxys
	Example Name 7 Preparation of zoledronic acid monohydrate A suspension of 1-imidazolylacetic acid (20g, 0. 159mol) and phosphorous acid (19.6g, 0. 239mol) in 1,2-dimethoxyethane (72m1) is heated to 75.deg. C for 30 minutes. The mixture is cooled to 35-40.deg. C and then gradually introduced phosphorous trichloride (48ml, 0. 543mol) while maintaining the temperature between 35-45.deg. C. The mixture is heated to 63-67.deg. C for 3 hrs, whereby white solid results. It is then cooled to 0-5.deg. C and quenched by slow addition of water (160ml) at 0-5.deg. C over a period of 1 hr. The resulting clear solution is heated at 100.deg. C for 3 hrs, cooled to ambient temperature and charcoalized. To the charcoalized solution is added acetone (320ml). The mixture is then stirred for 4 hours at 20-25.deg. C, the crystallized product is filtered, washed sequentially with chilled water (80ml), acetone (80ml) and dried in air oven at 55-60.deg. C until water content is between 6.2-7. 2percent w/w. Appearance: white crystalline solid, purity >99.5percent, meeting specification as per IHS. **Stage 1: With** anhydrous phosphorous acid **in** ethylene glycol dimethyl ether, Time= 0.5h, T= 75 °C **Stage 2: With** phosphorus trichoride **in** ethylene glycol dimethyl ether, Time= 3h, T= 35 - 67 °C **Stage 3: With** water **in** ethylene glycol dimethyl ether, Time= 8h, T= 0 - 100 °C **Patent**; **SUN PHARMACEUTICAL INDUSTRIES LIMITED**; WO2005/44831; (2005); (A2) English View in Reaxys
	Example Name 1.A Imidazol-1-ylacetic acid (50 gm), phosphorous acid (150 gm) and n-octane (1000 mL) were taken in a four necked round bottom flask fitted with an addition funnel, mechanical stirrer, condenser and thermometer pocket and allowed to stir at 90-95^{0}C. Phosphorus trichloride (250 gm) was then added to the reaction mixture and allowed to heat at 90-95^{0}C. The reaction mixture was cooled and distilled water (500 mL) was added to it. The reaction mixture was further heated to 90-95^{0}C and then cooled to room temperature, filtered through celite bed. Aqueous layer was separated and methanol (2000 mL) was EPO <DP n="11"/>added to it. The solution was cooled to 0-5 .deg.C and stirred for 4-5 hrs. The precipitated solid was filtered, washed with methanol and dried under vacuum yielding 70 gm of product. **Stage 1: With** anhydrous phosphorous acid **in** octane, T= 90 - 95 °C **Stage 2: With** phosphorus trichoride **in** octane, T= 90 - 95 °C **Stage 3: With** water **in** octane, T= 90 - 95 °C , Product distribution / selectivity **Patent**; **JUBILANT ORGANOSYS LIMITED**; WO2006/134603; (2006); (A1) English View in Reaxys
	Example Name 1.B Imidazol-1-ylacetic acid (50 gm), phosphorous acid (150 gm) and 1,4-dioxane (1000 mL) were taken in a four necked round bottom flask fitted with an addition funnel, mechanical stirrer, condenser and thermometer pocket and allowed to stir at 90-95^{0}C. Phosphorus trichloride (250 gm) was then added to the reaction mixture and allowed to heat at 90-

	95.deg.C. The reaction mixture was cooled and distilled water (500 mL) was added to it. The reaction mixture was further heated to 90-95^{0}C and then cooled to RT and filtered through celite bed. Methanol (2000 mL) was added to the filtrate and cooled to 0-5^{0}C and stirred for 4-5 hrs. The precipitated solid was filtered, washed with methanol and dried under vacuum to yield 56.0 gm of product. **Stage 1: With** anhydrous phosphorous acid **in** 1,4-dioxane, T= 90 - 95 °C **Stage 2: With** phosphorus trichoride **in** 1,4-dioxane, T= 90 - 95 °C **Stage 3: With** water **in** 1,4-dioxane, T= 90 - 95 °C , Product distribution / selectivity **Patent**; **JUBILANT ORGANOSYS LIMITED**; WO2006/134603; (2006); (A1) English View in Reaxys
	Example Name 3 Example- 3: Preparation of zoledronic acid; A mixture of imidazol-1-yl acetic acid (100 gm) and phosphorous acid (324 gm) was heated under stirring to about 60-80^{0}C to get a homogeneous solution. Phosphorous trichloride (324 gm) was added slowly at a temperature of about 75^{0}C to the homogeneous solution. The resultant mass was stirred for 6 hours and cooled. A solution of hydrochloric acid (9N, 465 ml) was added over 30 minutes and the entire mass was heated at 75-8O^{0}C for about 12 hours, treated with activated carbon (3.8 gm) and filtered. Acetone (1200 ml) was added to the filtrate and the resultant mixture was cooled to 15-2O^{0}C. After complete precipitation of the product, the mass was filtered and the wet cake was washed with acetone (300 ml) and dried at 50-6O^{0}C to get zoledronic acid as a white crystalline solid. Yield: 161 gmHPLC Purity: 99.92percent **Stage 1: With** anhydrous phosphorous acid, phosphorus trichoride, Time= 6h, T= 60 - 80 °C **Stage 2: With** hydrogenchloride, water, Time= 12.5h, T= 75 - 80 °C , Product distribution / selectivity **Patent**; **WOCKHARDT LTD; YADAV, Ram, Prasad; SHAIKH, Zakir Gafoor; MUKARRAM, Siddiqui Mohammad Jaweed; KUMAR, Yatendra**; WO2007/69049; (2007); (A2) English View in Reaxys
	Example Name 5 Example-5: Preparation of zoledronic acid; A mixture of imidazol-1-yl acetic acid (100 gm) and phosphorous acid (324 gm) was heated under stirring to about 60-80^{0}C to get a homogeneous solution. Phosphorous oxychloride (364 gm) was added slowly at a temperature of about 75^{0}C to the homogeneous solution. The resultant mass was stirred for 5 hours and cooled. A solution of hydrochloric acid (9N, 465 ml) was added over 30 minutes and the entire mass was heated at 9O^{0}C for about 12 hours, cooled and filtered. Acetone (1200 ml) was added to the filtrate and the resultant mixture was cooled to 15-2O^{0}C. After complete precipitation of the product, the mass was filtered and the <n="10"/>wet cake was washed with acetone (300 ml) and dried at 50-60^{0}C to get crystals of zoledronic acid.Yield: 170 gmHPLC Purity: 99.92percent **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate, Time= 5h, T= 60 - 80 °C **Stage 2: With** hydrogenchloride, water, Time= 12.5h, T= 90 °C , Product distribution / selectivity **Patent**; **WOCKHARDT LTD; YADAV, Ram, Prasad; SHAIKH, Zakir Gafoor; MUKARRAM, Siddiqui Mohammad Jaweed; KUMAR, Yatendra**; WO2007/69049; (2007); (A2) English View in Reaxys
	Example Name 1.A Example Title Preparation of Zoledronic Acid. Method - A. Imidazol-1-ylacetic acid (50 gm), phosphorous acid (150 gm) and n-octane (1000 mL) were taken in a four necked round bottom flask fitted with an addition funnel, mechanical stirrer, condenser and thermometer pocket and allowed to stir at 90-95 C. Phosphorus trichloride (250 gm) was then added to the reaction mixture and allowed to heat at 90-95 C.The reaction mixture was cooled and distilled water (500 mL) was added to it. The reaction mixture was further heated to 90-95 C. and then cooled to room temperature, filtered through celite bed. Aqueous layer was separated and methanol (2000 mL) was added to it. The solution was cooled to 0-5 C. and stirred for 4-5 hrs. he precipitated solid was filtered, washed with methanol and dried under vacuum yielding 70 gm of product. **Stage 1: With** anhydrous phosphorous acid, phosphorus trichoride **in** octane, T= 90 - 95 °C **Stage 2: With** water **in** octane, T= 90 - 95 °C , Product distribution / selectivity **Patent**; **Pandey, Satish Chandra; Haider, Hussain; Saxena, Sudhanshu; Singh, Manoj Kumar; Thaper, Rajesh Kumar; Dubey, Sushil Kumar**; US2009/312551; (2009); (A1) English View in Reaxys



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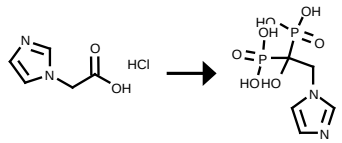
Yield	Conditions & References
89 %	Example Name 3 Example 3 - Zoledronic Acid Monohydrate; The raw humid zoledronic acid (equivalent to 90.3 g raw product), obtained according to Example 1, is suspended in water (3050 ml). The suspension is heated at reflux, with agitation. EPO <DP n="9"/>Water is added up to a total volume of 3750 ml, by which a total dissolution is obtained.The heating is then interrupted and the agitation, allowing it to slowly cool down to ambient temperature.Once the inside temperature is around 70 - 80^{0}C a frank crystallization starts.Once the ambient temperature is reached, it is cooled down to 2 - 5 ^{0}C, maintained at that temperature during 1 'Λ hours, filtered and the precipitate is washed with ice water.It is dried in a stove with air flow at 5.deg.C - 60 ^{0}C.169.3 g (89 percent) colorless crystals are obtained.The loss through dissection (6.8percent) confirms that this is a monohydrate.This substance, by diffraction with X-rays, dust method, presents peaks at the following values of 20 12.1; 12.8; 15.7; 18.9 +/- 0.2, coincident with those described for the form I (US 2005/0054616).Figure I A shows its diffractogram of dust X-rays and figure IV A the lay-out of the atoms in the unitary cell of the crystalline network for this form. **With** water, T= 70 - 80 °C , Heating / reflux **Patent**; **GADOR S.A.**; WO2007/16982; (2007); (A1) English View in Reaxys
	Example Name 5 Example 5: Process for Making the Crystalline Form of the Monohydrate of the Free Acid of Zoledronic Acid About 300 mg of the anhydrous form of zoledronic acid is suspended in about 1 mL of 96percent ethanol. The suspension is equilibrated for about 2 hours at about 60.deg.C. The solid precipitate is then isolated by filtration. **With** water **in** ethanol, Time= 2h, T= 60 °C **Patent**; **Novartis AG**; EP1925621; (2008); (A1) English View in Reaxys



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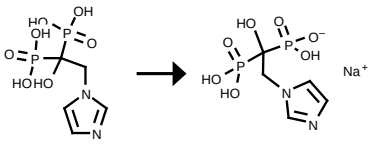
Yield	Conditions & References
74 - 79 %	Example Name 1; 4; 7 Examples; CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac); Preparation of ZLD-AC crystal form I; General procedure for the preparation of ZLD-AC crystal form I starting from 1- Imidazoleacetic acid (IAA), Phosphorous acid (H3PO3) and Phosphorous oxychloride (POC13) (Examples 1-9, see Table 1) :; A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-IMIDAZOLEACETIC acid (IAA), Phosphorous acid and a diluent (Toluene/Chlorobenzene/PEG-400/Silicon oil). The obtained suspension is heated to 75.deg.C-80.deg.C and Phosphorous oxychloride is added drop- wise. The reaction mixture is then heated to 75.deg.C-100.deg.C for 1-34 hours. Then water is added at 80.deg.C-100.deg.C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95.deg.C-100.deg.C for 13.5-19 hours. Then it is cooled to 5.deg.C and absolute Ethanol is added to obtain a precipitate after stirring at 5.deg.C for 2.5-4 hours [In some cases a precipitate of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50.deg.C for 17-24 hours to obtain Zoledronic acid crystal form I (LOD BY TGA=6. 3percent-9. 3percent).; ZLD HPLC METHOD: COLUMN: PHENOMENEX PHENYL-HEXYL 5UM, 250X4.6MM MOBILE PHASE: 40MM OCTANSULFONIC ACID SODIUM SALT IN 1percent HCLO4, 0.2percent H3PO4 : METHANOL (85:15) DETECTION: 220NM STABILITY WAS MEASURED VERSUS THE PRESENCE OF FORM II. P THE STABILITY DATA FOR EXAMPLE 4 IN THE TABLE ABOVE IS:

	Stage 1: With anhydrous phosphorous acid, trichlorophosphate **in** silicon oil, Time= 11 - 24h, T= 80 °C **Stage 2: With** water **in** toluene, silicon oil, Time= 16 - 19h, T= 80 - 100 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
69 %	Example Name 5 Examples; CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac); Preparation of ZLD-AC crystal form I; General procedure for the preparation of ZLD-AC crystal form I starting from 1- Imidazoleacetic acid (IAA), Phosphorous acid (H3PO3) and Phosphorous oxychloride (POC13) (Examples 1-9, see Table 1) :; A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-IMIDAZOLEACETIC acid (IAA), Phosphorous acid and a diluent (Toluene/Chlorobenzene/PEG-400/Silicon oil). The obtained suspension is heated to 75.deg.C-80.deg.C and Phosphorous oxychloride is added drop- wise. The reaction mixture is then heated to 75.deg.C-100.deg.C for 1-34 hours. Then water is added at 80.deg.C-100.deg.C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95.deg.C-100.deg.C for 13.5-19 hours. Then it is cooled to 5.deg.C and absolute Ethanol is added to obtain a precipitate after stirring at 5.deg.C for 2.5-4 hours [In some cases a precipitate of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50.deg.C for 17-24 hours to obtain Zoledronic acid crystal form I (LOD BY TGA=6. 3percent-9. 3percent).; ZLD HPLC METHOD: COLUMN: PHENOMENEX PHENYL-HEXYL 5UM, 250X4.6MM MOBILE PHASE: 40MM OCTANSULFONIC ACID SODIUM SALT IN 1percent HCLO4, 0.2percent H3PO4 : METHANOL (85:15) DETECTION: 220NM STABILITY WAS MEASURED VERSUS THE PRESENCE OF FORM II. P THE STABILITY DATA FOR EXAMPLE 4 IN THE TABLE ABOVE IS: **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** toluene, Time= 3h, T= 100 °C **Stage 2: With** water **in** toluene, Time= 16h, T= 80 - 100 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
58 %	Example Name 11 Example 11:; A 250ML three-necked flask equipped with a mechanical stirrer, a reflux condenser and A dropping funnel, was loaded with 1-IMIDAZOLEACETIC acid hydrochloride (4.9g, 0.03mole), phosphorous acid (4.9g, 0.06mole) and Silicon oil (MERCK) (27ml). The suspension was heated to 75.deg.C and phosphorous oxychloride (10. 5ML, 0. 1 lmole) was added drop-wise during 30 minutes. The reaction mixture was then heated to 80.deg.C for 27 hours. Then WATER (27ML) AND toluene (30ML) were added at 80.deg.C. The mixture was stirred vigorously for about 15 minutes. Then the toluene phase (containing the silicon oil) and the aqueous phase were separated. The aqueous phase was put in a clean flask and heated to 90.deg.C for 16 hours. Then it was cooled to room temperature and absolute Ethanol (27ML) was added during the cooling process to obtain a white precipitate immediately. The mixture was stirred at 5.deg.C for 4 hours. The white product was then filtered, washed with absolute Ethanol (2XL5ML) and dried in a vacuum oven at 50.deg.C for 24 hours to obtain 4.9g (58percent) of Zoledronic acid crystal form II (LOD by TGA=5. 2percent). **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** silicon oil, Time= 27.5h, T= 75 - 80 °C **Stage 2: With** water **in** toluene, silicon oil, Time= 16.25h, T= 80 - 90 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
38 %	Example Name 6 Examples; CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac); Preparation of ZLD-AC crystal form I; General procedure for the preparation of ZLD-AC crystal form I starting from 1- Imidazoleacetic acid (IAA), Phosphorous acid (H3PO3) and Phosphorous oxychloride (POC13) (Examples 1-9, see Table 1) :; A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-IMIDAZOLEACETIC acid (IAA), Phosphorous acid and a diluent (Toluene/Chlorobenzene/PEG-400/Silicon oil). The obtained suspension is heated to 75.deg.C-80.deg.C and Phosphorous oxychloride is added drop- wise. The reaction mixture is then heated to 75.deg.C-100.deg.C for 1-34 hours. Then water is added at 80.deg.C-100.deg.C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95.deg.C-100.deg.C for 13.5-19 hours. Then it is cooled to 5.deg.C and

	absolute Ethanol is added to obtain a precipitate after stirring at 5.deg.C for 2.5-4 hours [In some cases a precipitate of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50.deg.C for 17-24 hours to obtain Zoledronic acid crystal form I (LOD BY TGA=6. 3percent-9. 3percent).; ZLD HPLC METHOD: COLUMN: PHENOMENEX PHENYL-HEXYL 5UM, 250X4.6MM MOBILE PHASE: 40MM OCTANSULFONIC ACID SODIUM SALT IN 1percent HCLO4, 0.2percent H3PO4 : METHANOL (85:15) DETECTION: 220NM STABILITY WAS MEASURED VERSUS THE PRESENCE OF FORM II. P THE STABILITY DATA FOR EXAMPLE 4 IN THE TABLE ABOVE IS: **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** silicon oil, Time= 23h, T= 80 °C **Stage 2: With** water **in** silicon oil, Time= 16h, T= 80 - 100 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
	Example Name 2 Examples; CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac); Preparation of ZLD-AC crystal form I; General procedure for the preparation of ZLD-AC crystal form I starting from 1- Imidazoleacetic acid (IAA), Phosphorous acid (H3PO3) and Phosphorous oxychloride (POC13) (Examples 1-9, see Table 1) :; A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-IMIDAZOLEACETIC acid (IAA), Phosphorous acid and a diluent (Toluene/Chlorobenzene/PEG-400/Silicon oil). The obtained suspension is heated to 75.deg.C-80.deg.C and Phosphorous oxychloride is added drop- wise. The reaction mixture is then heated to 75.deg.C-100.deg.C for 1-34 hours. Then water is added at 80.deg.C-100.deg.C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95.deg.C-100.deg.C for 13.5-19 hours. Then it is cooled to 5.deg.C and absolute Ethanol is added to obtain a precipitate after stirring at 5.deg.C for 2.5-4 hours [In some cases a precipitate of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50.deg.C for 17-24 hours to obtain Zoledronic acid crystal form I (LOD BY TGA=6. 3percent-9. 3percent).; ZLD HPLC METHOD: COLUMN: PHENOMENEX PHENYL-HEXYL 5UM, 250X4.6MM MOBILE PHASE: 40MM OCTANSULFONIC ACID SODIUM SALT IN 1percent HCLO4, 0.2percent H3PO4 : METHANOL (85:15) DETECTION: 220NM STABILITY WAS MEASURED VERSUS THE PRESENCE OF FORM II. P THE STABILITY DATA FOR EXAMPLE 4 IN THE TABLE ABOVE IS: **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** chlorobenzene, Time= 1h, T= 100 °C **Stage 2: With** water **in** chlorobenzene, Time= 15.5h, T= 80 - 100 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
	Example Name 3 Examples; CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac); Preparation of ZLD-AC crystal form I; General procedure for the preparation of ZLD-AC crystal form I starting from 1- Imidazoleacetic acid (IAA), Phosphorous acid (H3PO3) and Phosphorous oxychloride (POC13) (Examples 1-9, see Table 1) :; A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-IMIDAZOLEACETIC acid (IAA), Phosphorous acid and a diluent (Toluene/Chlorobenzene/PEG-400/Silicon oil). The obtained suspension is heated to 75.deg.C-80.deg.C and Phosphorous oxychloride is added drop- wise. The reaction mixture is then heated to 75.deg.C-100.deg.C for 1-34 hours. Then water is added at 80.deg.C-100.deg.C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95.deg.C-100.deg.C for 13.5-19 hours. Then it is cooled to 5.deg.C and absolute Ethanol is added to obtain a precipitate after stirring at 5.deg.C for 2.5-4 hours [In some cases a precipitate of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50.deg.C for 17-24 hours to obtain Zoledronic acid crystal form I (LOD BY TGA=6. 3percent-9. 3percent).; ZLD HPLC METHOD: COLUMN: PHENOMENEX PHENYL-HEXYL 5UM, 250X4.6MM MOBILE PHASE: 40MM OCTANSULFONIC ACID SODIUM SALT IN 1percent HCLO4, 0.2percent H3PO4 : METHANOL (85:15) DETECTION: 220NM STABILITY WAS MEASURED VERSUS THE PRESENCE OF FORM II. P THE STABILITY DATA FOR EXAMPLE 4 IN THE TABLE ABOVE IS: **Stage 1: With** anhydrous phosphorous acid, trichlorophosphate **in** PEG-400, Time= 2h, T= 75 °C **Stage 2: With** water **in** PEG-400, toluene, Time= 13.5h, T= 80 - 100 °C , Product distribution / selectivity

	Patent; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
	Example Name I.iii Preparation of zoledronic acid. Into a 2L, three-necked RB flask was added 60g of imidazol-1-ylacetic acid hydrochloride prepared by the process described in step (ii), 105g of o-phosphoric acid and 250ml of ethylene dichloride. The reaction mass was heated to 50-55.deg.C and added 152g of phosphorous trichloride over a period of 2. 0-2. 5h keeping the temperature below 80.deg.C. After maintaining at 70-80.deg.C for 4h the reaction was quenched by adding 30ml of water and 165g of concentrated HC1. The reaction mass was heated to reflux temperature and maintained for 5-6h. The reaction mass was cooled to 25-30.deg.C, separated ethylene- dichloride layer, and treated the aqueous layer with carbon. Acetone (700ml) was added to the reaction mass and cooled to 5-10.deg.C. After maintaining for 2-3h reaction mass was filtered and the wet cake washed with 100ml of acetone. The Zoledronic acid so produced was dried at 50-60.deg.C to get 85g of white crystalline solid. Purity by HPLC is 98. 5percent. A small sample was dissolved in 20 times refluxing water and cooled to 25-30.deg.C. Pure zoledronic acid was isolated by filtration. Purity by HPLC is 99.4percent. **With** phosphoric acid, phosphorus trichoride **in** 1,2-dichloro-ethane, Time= 6 - 6.5h, T= 50 - 80 °C **Patent**; **NATCO PHARMA LIMITED; PULLA REDDY, Muddasani; USHA RANI, Vattikuti; VENKAIAH CHOWDARY, Nannapaneni**; WO2005/63717; (2005); (A1) English View in Reaxys
	Example Name 2 Preparation of zoledronic acid. Into a 2L, three-necked RB flask was added 60g of imidazol-1-ylacetic acid hydrochloride prepared by the process described in step (i) of the Example 1, 105g of o- phosphoric acid and 250ml of cyclohexane. The reaction mass was heated to 50-55.deg.C and added 152g of phosphorous trichloride over a period of 2. 0-2. 5h keeping the temperature below 80.deg.C. After maintaining at 80.deg.C for 6h, the reaction was quenched by adding 100 ml of water and 165g of concentrated HCI. The reaction mass was heated to reflux temperature and maintained for 5-6h. The reaction mass was cooled to 25-30.deg.C, separated cyclohexane layer, and treated the aqueous layer with carbon. Acetone (700ml) was added to the reaction mass and cooled to 5-10.deg.C. After maintaining for 2-3h reaction mass was filtered and the wet cake washed with 100ml of acetone. Crude zoledronic acid was dried at 50-60.deg.C to get 80g as white crystalline solid. Purity by HPLC is 98.0percent. The above crude zoledronic acid was taken into a 2L glass flask and added 1600ml of DM water. The reaction mass was heated to 90-95.deg.C and maintained for 2-3h to dissolve the solid. Carbon (lOg) was added to the reaction mass and filtered while hot. The filtrate was cooled to 25-30.deg.C and maintained for 3-4h before filtration. Wet cake was washed with water and dried at 50-60.deg.C till the moisture content reached 6-10percent. Yield of pure zoledronic acid, as monohydrate was 70g. Purity by HPLC is 99.3percent. **With** phosphoric acid, phosphorus trichoride **in** cyclohexane, Time= 8 - 8.5h, T= 50 - 80 °C **Patent**; **NATCO PHARMA LIMITED; PULLA REDDY, Muddasani; USHA RANI, Vattikuti; VENKAIAH CHOWDARY, Nannapaneni**; WO2005/63717; (2005); (A1) English View in Reaxys
	Example Name 3 Preparation of zoledronic acid. Into a 200L glass flask containing 10. 5kg of o-phosphoric acid and 25L of chlorobenzene was added 6. 0 kg of imidazol-1-ylacetic acid hydrochloride prepared by the process described in step (i) of the Example 1. The reaction mass was heated to 50-55 .deg.C and added 15.2 kg of phosphorous trichloride over a period of 2.0-2. 5hr keeping the temperature below 80 .deg.C. After maintaining at 60-80 .deg.C for 5hr the reaction was quenched by adding 3.0 L of water and 16.5 kg of concentrated HC1. The reaction mass was heated to reflux temperature and maintained for 5-6hr. The reaction mass was cooled to 25-30 .deg.C, separated chlorobenzene layer, and treated the aqueous layer with carbon. Acetone (70.0 L) was added to the reaction mass and cooled to 5-10 .deg.C. After maintaining for 2-3hr reaction mass was filtered and the wet cake washed with 10. 0 L of acetone. Crude zoledronic acid was dried at 50-60 .deg.C to get 8.0 kg as white crystalline solid. Purity by HPLC is 99. 0percent. The above crude zoledronic acid was taken into a 250-L, glass lined reactor and added 160 L of DM water. The reaction mass was heated to 90-95 .deg.C and maintained for 2-3hr to dissolve the solid. Carbon (1.0 kg) was added to the reaction mass and filtered while hot. The filtrate was cooled to 25-30 .deg.C and maintained for 3-4hr before filtration. Wet cake was washed with water and dried at 50-60 .deg.C till the moisture content reached 6- 10percent. Yield of pure zoledronic acid, as monohydrate was 7. 0 Kg. Purity by HPLC is 99.8percent. **With** phosphoric acid, phosphorus trichoride **in** chlorobenzene, Time= 7 - 7.5h, T= 50 - 80 °C

	Patent; **NATCO PHARMA LIMITED; PULLA REDDY, Muddasani; USHA RANI, Vattikuti; VENKAIAH CHOWDARY, Nannapaneni**; WO2005/63717; (2005); (A1) English View in Reaxys



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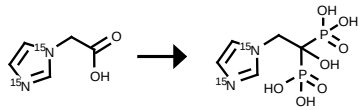
Yield	Conditions & References
99 %	Example Name 16 Example 16:; A 250ml flask was loaded with Zoledronic acid form I (4. 8G), Sodium hydroxide (0.7g) and Methanol (10 volumes per grams OF ZLD-AC) (48ML). The reaction mixture was heated to reflux temperature for 16 hours. Then it was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2X10ML) and dried in a vacuum oven at 50.deg.C for 22 hours to give 4.8g (99percent) of Zoledronate monosodium crystal form XV (LOD by TGA=0.8percent). Purity by HPLC 99. 9percent. **With** sodium hydroxide **in** methanol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
98 %	Example Name 37 Preparation of ZLD-NA crystal form XVI; Example 37:; A solution of sodium hydroxide (0.7g) in a mixture of water (50percent V/V)/ETHANOL (50percent v/v, 10 volumes per grams of ZLD-Ac form 1) (14ML) was added drop-wise to a suspension of Zoledronic acid (4. 8G) in a mixture of water (50percent V/V)/ETHANOL (50percent v/v, 10 volumes per grams of ZLD-Ac form I) (81ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice- bath. The precipitate was then filtered, washed with absolute Ethanol (2X20ML) and dried in a vacuum oven at 50.deg.C for 18 hours to give 5.2g (98percent) of Zoledronate monosodium crystal form XVI (LOD by TGA=9. 9percent). Purity by HPLC 99. 95percent. **With** sodium hydroxide **in** ethanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
96 %	Example Name 15 Preparation OF ZLD-AC crystal form XV; Example 15:; A 250ML flask was loaded with Zoledronic acid form I (4. 8G), Sodium hydroxide (0.7g) and absolute Ethanol (10 volumes per grams OF ZLD-AC) (48ML). The reaction mixture was heated to reflux temperature for 16 hours. Then it was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2X20ML) and dried in a vacuum oven at 50.deg.C for 23 hours to give 4. 9G (96percent) of Zoledronate monosodium crystal form XV in a mixture with Zoledronic acid crystal form I (LOD by TGA=5. 8percent). **With** sodium hydroxide **in** ethanol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
94 %	Example Name 38 Example 38 :; A solution of sodium hydroxide (0. 7g) in a mixture of WATER (50percent V/V)/IPA (50percent V/V, 10 volumes per grams of ZLD-Ac form I) (15ml) was added drop-wise to a suspension of Zoledronic acid (5. 0G) in A mixture of water (50percent V/V)/IPA (50percent v/v, 10 volumes per grams OF ZLD-AC form I) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (2x20ml) and dried in a vacuum oven at 50.deg.C for 24 hours to give 5.2g (94percent) of Zoledronate monosodium crystal form XVI (LOD by TGA=9.8percent). Purity by HPLC 99.9percent.

	With sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
89 %	Example Name 39 Example 39:; A solution of sodium hydroxide (0.7g) in a mixture of water (50percent v/v) /Methanol (50percent v/v, 10 volumes per grams OFZLD-AC form I) (14ML) was added drop-wise to a suspension of Zoledronic acid form I (4.8g) in a mixture of water (50percent V/V)/ETHANOL (50percent v/v, 10 volumes per grams OF ZLD-AC form 1) (81ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (LX25ML) and dried in a vacuum oven at 50.deg.C for 25.5 hours to give 4.8g (89percent) of Zoledronate monosodium crystal form XVI (LOD by TGA=11. 1percent). Purity by HPLC 99. 9percent. **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
83 %	Example Name 33 Example 33:; A solution of sodium hydroxide (0.7g) in a mixture of water (80percent V/V)/ETHANOL (20percent v/v, 10 volumes per grams of ZLD-Ac) (36ml) was added drop-wise to a suspension of Zoledronic acid form I (4. 8G) in a mixture of water (80percent v/v) /Ethanol (20percent v/v, 10 volumes per grams of ZLD-Ac) (202ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2X20ML) and dried in a vacuum oven at 50.deg.C for 22 hours to give 4.7g (83percent) of Zoledronate monosodium crystal form VIII (LOD by TGA=15. 5percent). Purity by HPLC 99.9percent **With** sodium hydroxide **in** ethanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
81 %	Example Name 34 Example 34:; A solution of sodium hydroxide (0.7g) in a mixture of water (80percent V/V)/METHANOL (20percent v/v, 10 volumes per grams OF ZLD-AC FPRM I) (36ML) was added drop-wise to a suspension of Zoledronic acid (4.8g) in a mixture of water (80percent V/V)/METHANOL (20percent v/v, 10 volumes per grams of ZLD-Ac form 1) (202ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (LX20ML) and dried in a vacuum oven at 50.deg.C for 22 hours to give 4.7g (81percent) OF ZOLEDRONATE monosodium crystal form VIII (LOD by TGA=16. 03percent). Purity by HPLC 99.9percent. **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
64 - 72 %	Example Name 31; 32 Example 31:; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10. Og) and water (247ML). The suspension was heated to 94.deg.C to obtain a clear solution. A 40percent aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to 4.deg.C during 2 hours and was stirred at this temperature for about 64 hours to obtain a massive precipitate. The white precipitate was filtered, washed with cold water (LXLOML) and dried in a vacuum oven at 50.deg.C for 26 hours to obtain 7.6g (64percent) of Zoledronate monosodium crystal form VIII (LOD by TGA=15. 1percent).; EXAMPLE 32- :; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10. Og) and water (247ML). The suspension was heated to 94.deg.C to obtain a clear solution. A 40percent aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to room temperature and stirred at this temperature for 16 hours. After cooling to 3.deg.C and stirring at this temperature for 1.5 hour, the white precipitate was filtered, washed with Methanol (2XL5ML) and dried in a vacuum oven at 50.deg.C for 25 hours to obtain 5.8g (49percent) of Zoledronate monosodium crystal form

	VIII (LOD by TGA=15. 1percent). The obtained Form VIII (2g) was recrystallized form water (34ml) to give 1.4g (72percent) of Zoledronic acid crystal form VIII (LOD) by TGA=11. 3percent). Purity by HPLC 100.0percent. **With** sodium hydroxide **in** water, Time= 17.5 - 66h, T= 3 - 94 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
10 - 79 %	Example Name 35; 36 Example 35 :; A solution of sodium hydroxide (0.7g) in a mixture of water (80percent v/v)/IPA (20percent v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid (5. 0G) in a mixture of water (80percent v/v)/IPA (20percent v/v, 10 volumes per grams OF ZLD-AC FONN I) (212ML) AT REFLUX temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (2X20ML) and dried in a vacuum oven at 50.deg.C for 24 hours to give 4.7g (79percent) of Zoledronate monosodium crystal form VIII (LOD by TGA=15. 40percent). Purity by HPLC 99.95percent.; Example 36:; A solution of sodium hydroxide (0.7g) in a mixture of water (60percent V/V)/IPA (40percent v/v, 10 volumes per grams of ZLD-Ac form I) (19ml) was added drop-wise to A suspension of Zoledronic acid (5. 0G) in a mixture of water (60percent V/V)/ IPA (40percent v/v, 10 volumes per grams OF ZLD-AC FORM I) (106ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (LX20ML) AND dried in a vacuum oven at 50.deg.C for 27 hours to give 0.6g (10percent) of Zoledronate monosodium crystal form VIII (LOD by TGA=15.0percent). **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
	Example Name 40 Preparation of ZLD-Na crystal form XVII; Example 40:; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10. 0G) and water (247ML). The suspension was heated to 94.deg.C to obtain a clear solution. A 29percent aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to room temperature and stirred at this temperature for 16 hours. After cooling to 3.deg.C the product was isolated by filtration. Further cooling of the mother-liquid led to the formation of A white precipitate. The precipitate was filtered and dried in a vacuum oven at 50.deg.C for 24 hours to obtain 0. 6G of Zoledronate monosodium crystal form XVII (LOD by TGA=10. 3percent). **With** sodium hydroxide **in** water, Time= 16h, T= 20 - 94 °C , Heating / reflux **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
	Example Name 72 General procedure for the preparation of amorphous Zoledronate sodium; Example 72:; A 100ML flask was loaded with Zoledronic acid crystal form XII (2. 0g), Sodium hydroxide (0. 57G) and water (lOml). The reaction mixture was stirred at room temperature to obtain a clear solution. Then the solution was concentrated under vacuum to obtain a precipitate. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with water (2XLOML) and dried in a vacuum oven at 50.deg.C for 24 hours to give 0.76g of amorphous Zoledronate sodium. **With** sodium hydroxide **in** water, T= 20 °C **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
	Example Name 30 CRYSTAL FORMS OF ZOLEDRONATE MONOSODIUM (ZLD-NA); Preparation OL : ZLD-NA CRYSTAL FORM VI1 [I; Example 30 :; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer and a reflux condenser was loaded with Zoledronic acid form I (10.0g) and water (247ML). THE suspension was heated to 94.deg.C to obtain a clear solution. Sodium hydroxide (pearls, 1. 42g) was added. A pH test of the sodium salt showed PH=4. 54. The solution

	was cooled to 60.deg.C and IPA (10. 5ML) was added. The reaction mixture was cooled to room temperature during 2 hours and was stirred at this temperature for about 64 hours. After cooling to 5.deg.C and stirring at this temperature for 1 hour, the white precipitate was filtered, washed with cold water (LXLOML) and dried in a vacuum oven at 50.deg.C for 23.5 hours to obtain 7. 0g of Zoledronate monosodium crystal form VIII (pH=4. 32). Purity by HPLC 100.0percent. **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 67h, T= 5 - 94 °C , pH= 4.54, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys



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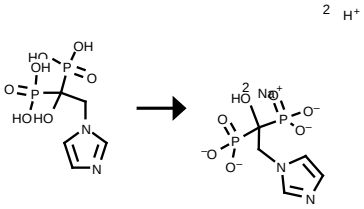
Yield	Conditions & References
26 %	**Stage 1: With** orthophosphorus acid, trichlorophosphate **in** toluene, Time= 5h, T= 80 °C **Stage 2: With** hydrogenchloride, Time= 1h, Heating, Further stages. **Mao, Junhong; Mukherjee, Sujoy; Zhang, Yong; Cao, Rong; Sanders, John M.; Song, Yongcheng; Zhang, Yonghui; Meints, Gary A.; Gao, Yi Gui; Mukkamala, Dushyant; Hudock, Michael P.; Oldfield, Eric**; Journal of the American Chemical Society; **vol.** 128; nb. 45; (2006); p. 14485 - 14497 View in Reaxys
26 %	**Stage 1: With** orthophosphorus acid, trichlorophosphate **in** toluene, Time= 5h, T= 80 °C **Stage 2: With** hydrogenchloride, Time= 6h, Further stages. **Mukherjee, Sujoy; Song, Yongcheng; Oldfield, Eric**; Journal of the American Chemical Society; **vol.** 130; nb. 4; (2008); p. 1264 - 1273 View in Reaxys



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Yield	Conditions & References
99 %	Example Name 62 Preparation OFZLD-NA2 CRYSTAL FORM XXV; Example 62:; A solution of sodium hydroxide (1.4g) in a mixture of water (80percent v/v)/Methanol (20percent V/V, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid form I (5. 0G) in A mixture of water (80percent V/V)/METHANOL (20percent V/V, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at REFLUX temperature for additional 19 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice- bath. The solution was then evaporated to dryness to obtain 6. LG (99percent) of Zoledronate disodium crystal form XXV (LOD by TGA=7.4percent). Purity by HPLC 99.9percent. **With** sodium hydroxide **in** methanol, water, Time= 19h, Heating / reflux **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
98 %	Example Name 55 Example 55:; A solution of sodium hydroxide (1.4g) in a mixture of water (80percent V/V)/ETHANOL (20percent v/v, 10 volumes per grams OF ZLD-AC form 1) (38ML) was added drop-wise to a suspension of Zoledronic acid form I (5. 0G) in a mixture of water (80percent v/v)/Ethanol (20percent v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 18. 5 hours. Then the reaction mixture

	was cooled to room temperature and the solution was evaporated to dryness to obtain 6.7g (98percent) of Zoledronate disodium crystal form VII (LOD by TGA=16. 8percent). Purity by HPLC 99. 9percent. **With** sodium hydroxide **in** ethanol, water, Time= 18.5h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
97 %	Example Name 59 Example 59 :; A solution of sodium hydroxide (1. 4g) in a mixture of water (20percent V/V)/METHANOL (80percent v/v, 10 volumes per grams of ZLD-Ac form 1) (lOml) was added drop-wise to a suspension of Zoledronic acid form I (5. 0G) in a mixture of water (20percent v/v)/Methanol (80percent v/v, 10 volumes per grams OFZLD-AC) (53ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 17 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice- bath. The precipitate was then filtered, washed with Methanol (1X10M1) and dried in a vacuum oven at 50.deg.C for 26 hours to give 5.6g (97percent) of Zoledronate disodium crystal form XIV (LOD by TGA=1.4percent). Purity by HPLC 99.9percent. **With** sodium hydroxide **in** methanol, water, Time= 17h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
94 - 96 %	Example Name 44 Example 44 :; A solution of sodium hydroxide (1.4g) in a mixture of WATER (Xpercent V/V)/ETHANOL (Ypercent v/v, 10 volumes per grams of ZLD-Ac form 1) (10-15ML) was added drop-wise to a suspension of Zoledronic acid fomr I (5. 0G) in a mixture of water (Xpercent V/V)/ETHANOL (Ypercent v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.9percent.) **With** sodium hydroxide **in** ethanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
94 %	Example Name 45 Example 45:; A solution of sodium hydroxide (1.4g) in a mixture of water (Xpercent V/V)/METHANOL (Ypercent v/v, 10 volumes per grams OF ZLD-AC FORM I) (15ML) was added drop-wise to a suspension of Zoledronic acid form I (5. 0G) in a mixture of water (Xpercent V/V)/METHANOL (Ypercent v/v, 10 volumes per grams of ZLD-Ac) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice- bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.95percent. **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
93 %	Example Name 63 Preparation OF ZLD-NA2 crystal form XXVII; Example 63:; A 100ml flask was loaded with Zoledronic acid form I (4.9g), Sodium hydroxide (1.4g), Methanol (50ML) and water (2. 5ML) [= 5percent v/v water in Methanol]. The reaction mixture was heated to reflux temperature for 21 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2X75ML) and dried in a vacuum oven at 50.deg.C for 27.5 hours to give 5. 7G (93percent) of Zoledronate disodium crystal form XXVII (LOD by TGA=5.3percent). Purity by HPLC 99. 9percent. **With** sodium hydroxide **in** methanol, water, Time= 21h, Heating / reflux, Product distribution / selectivity

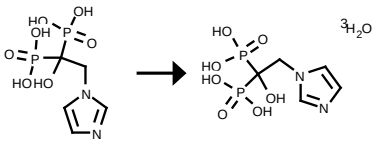
	Patent; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
92 %	Example Name 58 Preparation of ZLD-NA2 crystal form XIV; Example 58 :; A solution of sodium hydroxide (0. 7g) in a mixture of water (20percent V/V)/DMF (80percent v/v, 10 volumes per grams of ZLD-Ac form XII) (1 Oml) was added drop-wise to a suspension of Zoledronic acid form XII (4. 98G) in a mixture of water (20percent V/V)/DMF (80percent v/v, 10 volumes per grams OF ZLD-AC) (53ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with DMF (2X 1 OML) and dried in a vacuum oven at 50.deg.C for 24 hours to give 4. 8g (92percent) of Zoledronate disodium crystal form XIV (LOD by TGA=1.9percent). **With** sodium hydroxide **in** DMF (N,N-dimethyl-formamide), water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
91 %	Example Name 56 Preparation OF ZLD-NA2 crystal form X; Example 56:; A solution of sodium hydroxide (0.7g) in a mixture of water (20percent V/V)/IPA (80percent v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4. 98G) in A mixture of water (20percent V/V)/IPA (80percent V/V, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (LX25ML) and dried in a vacuum oven at 50.deg.C for 24 hours to give 4. 7G (91 percent) of Zoledronate disodium crystal form X (LOD by TGA=2. 6percent). **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
90 - 91 %	Example Name 46 Example 46:; A solution of sodium hydroxide (1.4g) in a mixture of water (Xpercent V/V)/IPA (Ypercent V/V, 10 volumes per grams of ZLD-Ac form I) (10-15ml) was added drop-wise to a suspension of Zoledronic acid (5. 0g) in a mixture of water (Xpercent V/V)/IPA (Ypercent v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.95percent. **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
90 %	Example Name 64 Example 64 :; A solution of sodium hydroxide (0. 7g) in a mixture of water (20percent V/V)/METHANOL (80percent V/V, 10 volumes per grams OF ZLD-AC form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (20percent V/V)/ Methanol (80percent v/v, 10 volumes per grams OF ZLD-AC) (53ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2X 15ML) and dried in a vacuum oven at 50.deg.C for 24 hours to give 4. 85g (90percent) of Zoledronate disodium crystal form XXVII (LOD by TGA=7.5percent). **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys

89 - 91 %	Example Name 41 CRYSTAL FORMS ORMS OF ZOLEDRONATE DISODIUM (ZLD-Na2) PREPARATION OF ZTI I)-NA2 CRYSTAL FORM V; EXAMPLE 41 :; A solution of sodium hydroxide (0.7g) in a mixture of water (Xpercent V/V)/ETHANOL (Ypercent v/v, 10 volumes per grams OF ZLD-AC FORM XIP (10-15ML) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (Xpercent V/V)/ETHANOL (Ypercent v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form V. **With** sodium hydroxide **in** ethanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
89 %	Example Name 53 Example 53:; A solution of sodium hydroxide (0.7g) in a mixture of water (80percent V/V)/ETHANOL or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac fonn XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (80percent V/V)/ETHANOL or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD- Ac) (212ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form VII **With** sodium hydroxide **in** ethanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
86 %	Example Name 47 Preparation of ZLD-Na2 crystal form VI; Example 47 ;: A solution of sodium hydroxide (0. 7g) in a mixture of water (60percent V/V)/ETHANOL or Methanol (40percent v/v, 10 volumes per GRAMS OFZLD-AC form XII) (19ML) was added drop- wise to a suspension OF ZOLEDROLLIC acid form XII (4. 98G) in A mixture of water (60percent v/v) / Ethanol or Methanol (40percent v/v, 10 volumes per grams OF ZLD-AC) (106ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form VI **With** sodium hydroxide **in** ethanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
85 %	Example Name 43 Example 43:; -A solution of sodium hydroxide (0. 7g) in a mixture of water (Xpercent V/V)/IPA (Ypercent v/v, 10 volumes per grams of ZLD-Ac form XII) (13-15ML) was added drop-wise to a suspension of Zoledronic acid (4.98g) in a mixture of water (Xpercent V/V)/IPA (Ypercent v/v, 10 volumes per grams OFZLD-AC FORM XII) (70-85ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form V. **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
85 %	Example Name 53 Example 53:; A solution of sodium hydroxide (0.7g) in a mixture of water (80percent V/V)/ETHANOL or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac fonn XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (80percent V/V)/ETHANOL or Methanol or IPA (20percent v/v, 10

	volumes per grams of ZLD- Ac) (212ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form VII **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
85 - 88 %	Example Name 42 fExample 42:; A solution of sodium hydroxide (0.7g) in a mixture of water (Xpercent v/v)/Methanol (Ypercent v/v, 10 volumes per grams OF ZLD-AC form XII) (13-15ML) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (Xpercent V/V)/ Methanol (Ypercent v/v, 10 volumes per grams of ZLD-Ac) (70-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form V **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
84 %	Example Name 57 Preparation OF ZLD-NAZ crystal form XIII; Example 57:; A solution of sodium hydroxide (1.4g) in a mixture of water (5percent V/V)/ETHANOL (95percent v/v, 10 volumes per grams of ZLD-Ac form I) (8ml) was added drop-wise to a suspension of Zoledronic acid form I (5. 0G) in a mixture of water (5percent V/V)/ETHANOL (95percent V/V, 10 volumes per grams of ZLD-Ac) (45ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 19.5 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Ethanol (LXLOML) and dried in a vacuum oven at 50.deg.C for 20 hours to give 4.9g (84percent) OF ZOLEDRONATE DISODIUM crystal form XIII (LOD by TGA=3.4percent). Purity by HPLC 99.9percent. **With** sodium hydroxide **in** ethanol, water, Time= 19.5h, Heating / reflux **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
83 %	Example Name 53 Example 53:; A solution of sodium hydroxide (0.7g) in a mixture of water (80percent V/V)/ETHANOL or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac fonn XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (80percent V/V)/ETHANOL or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD- Ac) (212ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form VII **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
78 %	Example Name 48 Example 48:; A solution of sodium hydroxide (1. 4g) in a mixture of water (80percent v/v) /IPA (20percent v/v, 10 volumes per grams OF ZLD-AC FORM I (8ML) was added drop-wise to a suspension of Zoledronic acid FORM I (5. 0g) in a mixture of water (80percent v/v) /IPA (20percent v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature and the solution was evaporated to dryness. The obtained solid was dried in a vacuum oven at 50.deg.C for 5 hours to give 5. 2G (78percent) of Zoledronate disodium crystal form VI (LOD by TGA=15. 4percent). Purity by HPLC 99.9percent.

	With sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
78 %	Example Name 47 7Preparation of ZLD-Na2 crystal form VI; Example 47 :; A solution of sodium hydroxide (0. 7g) in a mixture of water (60percent V/V)/ETHANOL or Methanol (40percent v/v, 10 volumes per GRAMS OFZLD-AC form XII) (19ML) was added drop- wise to a suspension OF ZOLEDROLLIC acid form XII (4. 98G) in A mixture of water (60percent v/v) / Ethanol or Methanol (40percent v/v, 10 volumes per grams OF ZLD-AC) (106ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate disodium crystal form VI **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
24 %	Example Name 50 Preparation of ZLD-Na2 crystal form VII; Example 50:; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer and a reflux condenser was loaded with Zoledronic acid form I (10. OG) and water (260ml). The suspension was heated to 80.deg.C to obtain a clear solution. Sodium hydroxide (pearls, 2. 84g) was added. A pH test of the sodium salt showed PH=7. 35. The solution was cooled to 60.deg.C and IPA (10. 5ML) was added. The reaction mixture was cooled to room temperature during 2 hours and was stirred at this temperature for about 16 hours. After cooling to 5.deg.C and stirring at this temperature for 2 hours, the solution was evaporated to dryness to obtain a white solid. The obtained solid was reslurred in water (50ML) and cooled to 4.deg.C. The product was then isolated by filtration and dried in a vacuum oven at 50.deg.C for 24 hours to obtain 3.2g of Zoledronate disodium crystal form VII (24percent) (pH=7.27). Purity by HPLC 100.0percent. **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 20h, T= 5 - 80 °C , pH= 7.35, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
22 - 23 %	Example Name 51; 52 Example 51:; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10. OG) and water (130ML). The suspension was heated to reflux temperature to obtain a clear solution. A 40percent ; aqueous solution of Sodium hydroxide (6. 9g) was added drop-wise. The solution was then cooled to 4.deg.C during 2 hours and was stirred at this temperature for about 1.5 hours. The solution was concentrated to half of its volume to obtain a precipitate. The white precipitate was filtered and dried in a vacuum oven at 50.deg.C for 22 hours to obtain 2.7g (22percent) of Zoledronate disodium crystal form VII (LOD by TGA=10.7percent).; Example 52:; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and A dropping funnel, was loaded with Zoledronic acid form I (10. OG) and water (130ML). The suspension was heated to reflux temperature (92.deg.C) to obtain A clear solution. A 40percent aqueous solution of Sodium hydroxide (6.9g) was added drop-wise. The solution was then cooled to 25.deg.C was stirred at this temperature for about 16 hours. The solution was then concentrated to half of its volume to obtain a precipitate. The white precipitate was filtered and dried in a vacuum oven at 50.deg.C for 18.5 hours to obtain 2. 8g (23percent) of Zoledronate disodium crystal form VII (LOD by TGA=10. 2percent). Purity by HPLC 100.0percent. **With** sodium hydroxide **in** water, Time= 3.5 - 16h, T= 4 - 92 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
	Example Name 61 Example 61:; A 0. 5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (20. 0G) and water (260ML). The suspension was heated to reflux temperature (92.deg.C) to obtain a clear solution. A 40percent aqueous solution of Sodium hydroxide (13. 8g) was added drop-wise. The solution was then cooled to 25.deg.C and was stirred at this temperature for about 16 hours.

	The solution was then concentrated to half of its volume to obtain a precipitate. After stirring at 0.deg.C for 72 hours, the white precipitate was filtered and dried in a vacuum oven at 50.deg.C for 23 hours to obtain 10.4g of Zoledronate disodium crystal form XIX. **With** sodium hydroxide **in** water, Time= 16h, T= 25 - 92 °C , Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys



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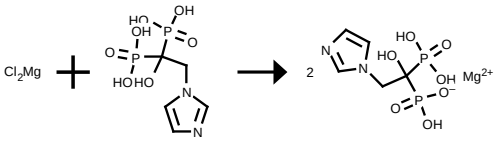
Yield	Conditions & References
	Example Name 1 Example Title Preparation of Zoledronic Acid Trihydrate 5 g of anhydrous zoledronic acid was taken into a round bottomed flask equipped with a magnetic stirrer, condenser and oil bath, then 150 ml of water was added to it. The reaction mass was heated slowly to 73.deg. C. to obtain a clear solution. The solution was filtered while hot to make it particle free. The clear filtrate was taken into a fresh round-bottomed flask and allowed to cool to 30.deg. C. The reaction mass was stirred at 30.deg. C. for 10 minutes. The separated solid was filtered under vacuum. The compound was suction dried under a vacuum of 600 mm Hg for 10 minutes to get 3.6 g of the title compound. Samples of this product were analyzed, to generate all of FIGS. 1-6. Moisture content: 15.5percent (w/w). Melting point: 238+/-3.deg. C. **With** water, Time= 0.166667h, T= 30 - 73 °C **Patent**; **Mohakhud, Pradeep Kumar; Murki, Veerender; Nandanmudi, Kishore Babu; Babu, Moses; Banerjee, Surajit**; US2006/178439; (2006); (A1) English View in Reaxys
	Example Name 2 Example 2 - Zoledronic Acid Trihydrate; The raw humid zoledronic acid (equivalent to 30 g dry product), obtained in Example 1, is suspended in water (900 ml).The suspension is heated at reflux, thus obtaining a solution. EPO <DP n="8"/>This hot solution is slowly added and blended to a refrigerated container, containing water (50 ml).The inside temperature is adjusted by means of the flow of the refrigerant fluid and the volume of aggregate of the hot concentrated solution, in order to keep it between 15 and 25 ^{0}C.The aggregate requires around VA hours.Once all the zoledronic acid solution is added, it is cooled down to 0 - 5 ^{0}C maintaining this temperature over 2 - 3 hours, it is filtered, washed with ice water (30 ml) and dried with air flow at 50 - 60^{0}C.The obtained product presents the following physicochemical characteristics.Diffraction by X-rays (dust method)It presents peaks in at following values of 2Ψ 9.2; 10.4; 14.7; 16.4 .deg. +/- 0.2.deg..The diffractogram is the one shown in Figure I.Titre (potentiometric): 99 percentHumidity (Loss by dissection): 16.6 percentTGA_(Thermogravimetric Analysis):The obtained curve is shown in Figure II.DSC (Differential Scanning Calorimetry)The obtained curve is shown in Figure II.Infrared Spectrum (KBr)Absorption at 3578-3011; 1643.6; 1579.9; 1549.1; 1443.0; 1414.0; 1387.0; 1294.4; 1155.5; 966.5 cm^{-1}Corresponds to Figure III. **With** water, Time= 3.5h, T= 15 - 25 °C , Heating / reflux **Patent**; **GADOR S.A.**; WO2007/16982; (2007); (A1) English View in Reaxys
	Example Name 1 EXAMPLE 1; PREPARATION OF ZOLEDRONIC ACID TRIHYDRATE5 g of anhydrous zoledronic acid was taken into a round bottomed flask equipped with a magnetic stirrer, condenser and oil bath, then 150 ml of water EPO <DP n="16"/>was added to it. The reaction mass was heated slowly to 73.deg. C to obtain a clear solution. The solution was filtered while hot to make it particle free. The clear filtrate was taken into a fresh round-bottomed flask and allowed to cool to 30.deg. C. The reaction mass was stirred at 30.deg. C for 10 minutes. The separated solid was filtered under vacuum. The compound was suction dried under a vacuum of 600 mm Hg for 10 minutes to get 3.6 g of the title compound.Samples of this product were analyzed, to generate all of Figs. 1-6. Moisture content: 15.5 percent (w/w) by the Karl Fischer method. Melting point: 238 +/- 3.deg. C.

	With water, Time= 0.166667h, T= 30 °C **Patent**; **DR. REDDY'S LABORATORIES LTD.; DR. REDDY'S LABORATORIES, INC.**; WO2007/32808; (2007); (A1) English View in Reaxys



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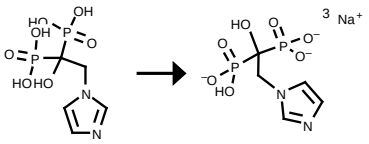
Yield	Conditions & References
	Example Name 4 Example Title Example 4 Example 4 Process for Making the Crystalline Form of the 1:2 Magnesium Salt of Zoledronic Acid In a 500 mL three-necked flask, 2.9 g zoledronic acid are dissolved in 80 mL water and 10 mL NaOH 2 N. To this solution a solution of 0.408 g magnesium chloride hexahydrate in 80 mL ethanol is added at room temperature. The product crystallizes slowly during stirring the reaction mixture at room temperature. After stirring for some hours, the formed white precipitate is filtrated and washed with ethanol. Drying over night in a vacuum oven gives 2.79 g of a white product with the following composition: C: 17.87; H: 3.22; N: 8.22; P: 18.6; Mg: 1.45; H_2O: 7.73. **With** sodium hydroxide **in** water, T= 20 °C **Patent**; **Novartis AG**; EP1925621; (2008); (A1) English View in Reaxys



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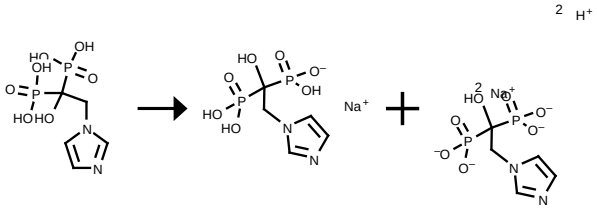
Yield	Conditions & References
84 %	Example Name 70 Preparation of ZLD-Na3 crystal form XI; Example 70:; A 250ML flask was loaded with Zoledronic acid form XII (5. 0G), Sodium hydroxide (1.4g), absolute Ethanol (50ML) and water (2. 5ML) [= 5percent v/v water in Ethanol]. The reaction mixture was heated to reflux temperature for 20 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2X25ML) and dried in a vacuum oven at 50.deg.C for 24 hours to give 5.4g (86percent) of Zoledronate trisodium crystal form XI (LOD by TGA=8. 9percent). **With** sodium hydroxide **in** ethanol, water, Time= 20h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
79 - 85 %	Example Name 65; 66; 67; 68; 69 PREPARATION OF ZLD-NA3 CRYSTAL FORM IX; Example 65:; A solution of sodium hydroxide (1.4g) in a mixture of water (20percent V/V)/ETHANOL or Methanol or IPA (80percent v/v, 10 volumes per grams OF ZLD-AC FORM XII) (LOML) WAS added drop-wise to a suspension of Zoledronic acid form XII (5. 0g) in A mixture of water (20percent v/v) /Ethanol or Methanol or IPA (80percent v/v, 10 volumes per grams of ZLD-Ac) (53ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX; Example 66:; A solution of sodium hydroxide (1.4g) in a mixture of water (40percent V/V)/ETHANOL or Methanol or IPA (60percent v/v, 10 volumes per grams of ZLD-Ac form XII) (13ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (40percent v/v) /Ethanol or Methanol or IPA (60percent v/v, 10 volumes per grams OF ZLD-

	AC) (71ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX; TExample 67 :; A solution of sodium hydroxide (1.4g) in a mixture of water (50percent V/V)/ETHANOL or Methanol or IPA (50percent v/v, 10 volumes per grams of ZLD-Ac form XII) (15ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (50percent V/V)/ETHANOL or Methanol or IPA (50percent v/v, 10 volumes per grams OF ZLD-AC) (85ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX.; tqExample 68: A solution of sodium hydroxide (1.4g) in a mixture of water (60percent V/V)/ETHANOL or Methanol or IPA (40percent v/v, 10 volumes per grams OF ZLD-AC FORM XI (L9ML) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (60percent V/V)/ETHANOL or Methanol or IPA (40percent v/v, 10 volumes per grams OF ZLD-AC) (106ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX. ; sExample 69 :; A solution of sodium hydroxide (1. 4g) in A mixture of water (80percent v/v)/Ethanol or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac form XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0g) in a mixture of water (80percent v/v)/Ethanol or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
64 - 88 %	Example Name 65; 66; 67; 68; 69 PREPARATION OF ZLD-NA3 CRYSTAL FORM IX; Example 65:; A solution of sodium hydroxide (1.4g) in a mixture of water (20percent V/V)/ETHANOL or Methanol or IPA (80percent v/v, 10 volumes per grams OF ZLD-AC FORM XII) (LOML) WAS added drop-wise to a suspension of Zoledronic acid form XII (5. 0g) in A mixture of water (20percent v/v) /Ethanol or Methanol or IPA (80percent v/v, 10 volumes per grams of ZLD-Ac) (53ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX; Example 66:; A solution of sodium hydroxide (1.4g) in a mixture of water (40percent V/V)/ETHANOL or Methanol or IPA (60percent v/v, 10 volumes per grams of ZLD-Ac form XII) (13ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (40percent v/v) /Ethanol or Methanol or IPA (60percent v/v, 10 volumes per grams OF ZLD-AC) (71ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX; TExample 67 :; A solution of sodium hydroxide (1.4g) in a mixture of water (50percent V/V)/ETHANOL or Methanol or IPA (50percent v/v, 10 volumes per grams of ZLD-Ac form XII) (15ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (50percent V/V)/ETHANOL or Methanol or IPA (50percent v/v, 10 volumes per grams OF ZLD-AC) (85ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX.; tqExample 68: A solution of sodium hydroxide (1.4g) in a mixture of water (60percent V/V)/ETHANOL or Methanol or IPA (40percent v/v, 10 volumes per grams OF ZLD-AC FORM XI (L9ML) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (60percent V/V)/ETHANOL or Methanol or IPA (40percent v/v, 10 volumes per grams OF ZLD-AC) (106ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX. ; sExample 69 :; A solution of sodium hydroxide (1. 4g) in A mixture of water (80percent v/v)/Ethanol or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac form XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0g) in a mixture of water (80percent v/v)/Ethanol or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate

	was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX **With** sodium hydroxide **in** methanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys
58 - 84 %	Example Name 65; 66; 67; 68; 69 PREPARATION OF ZLD-NA3 CRYSTAL FORM IX; Example 65:; A solution of sodium hydroxide (1.4g) in a mixture of water (20percent V/V)/ETHANOL or Methanol or IPA (80percent v/v, 10 volumes per grams OF ZLD-AC FORM XII) (LOML) WAS added drop-wise to a suspension of Zoledronic acid form XII (5. 0g) in A mixture of water (20percent v/v) /Ethanol or Methanol or IPA (80percent v/v, 10 volumes per grams of ZLD-Ac) (53ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX; Example 66:; A solution of sodium hydroxide (1.4g) in a mixture of water (40percent V/V)/ETHANOL or Methanol or IPA (60percent v/v, 10 volumes per grams of ZLD-Ac form XII) (13ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (40percent v/v) /Ethanol or Methanol or IPA (60percent v/v, 10 volumes per grams OF ZLD-AC) (71ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX; TExample 67 :; A solution of sodium hydroxide (1.4g) in a mixture of water (50percent V/V)/ETHANOL or Methanol or IPA (50percent v/v, 10 volumes per grams of ZLD-Ac form XII) (15ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (50percent V/V)/ETHANOL or Methanol or IPA (50percent v/v, 10 volumes per grams OF ZLD-AC) (85ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX.; tqExample 68: A solution of sodium hydroxide (1.4g) in a mixture of water (60percent V/V)/ETHANOL or Methanol or IPA (40percent v/v, 10 volumes per grams OF ZLD-AC FORM XI (L9ML) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0G) in a mixture of water (60percent V/V)/ETHANOL or Methanol or IPA (40percent v/v, 10 volumes per grams OF ZLD-AC) (106ML) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX. ; sExample 69 :; A solution of sodium hydroxide (1. 4g) in A mixture of water (80percent v/v)/Ethanol or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac form XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (5. 0g) in a mixture of water (80percent v/v)/Ethanol or Methanol or IPA (20percent v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate trisodium crystal form IX **With** sodium hydroxide **in** ethanol, water, Time= 16h, Heating / reflux, Product distribution / selectivity **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys



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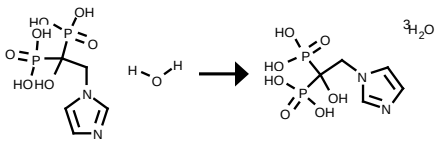
Yield	Conditions & References
13 %	Example Name 54

	Example 54 :; A solution of sodium hydroxide (0.7g) in a mixture of water (60percent v/v)/IPA (40percent v/v, 10 volumes per grams of ZLD-Ac form XII) (19ml) was added drop-wise to A suspension of Zoledronic acid form XII (4.98g) in A mixture of water (60percent v/v)/IPA (40percent v/v, 10 volumes per grams of ZLD-Ac) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (LX20ML) and dried in a vacuum oven at 50.deg.C for 24 hours to give Zoledronate monosodium crystal form VIII (crop I). Then the precipitate from the mother-liquid was isolated by filtration as well, and dried in a vacuum oven at 50.deg.C for 24 hours to give 2. 8g (13percent) of Zoledronate disodium crystal form VII (crop II). **With** sodium hydroxide **in** water, isopropyl alcohol, Time= 16h, Heating / reflux **Patent**; **TEVA PHARMACEUTICAL INDUSTRIES LTD.; TEVA PHARMACEUTICALS USA, INC.**; WO2005/5447; (2005); (A2) English View in Reaxys



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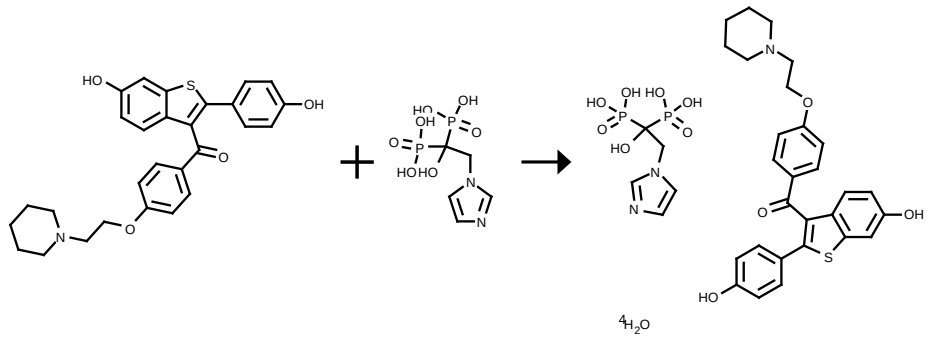
Yield	Conditions & References
	Example Name 6 Example 6: Process for Making the Crystalline Form of the Trihydrate of the Free Acid of Zoledronic Acid About 500 mg of the monohydrate of zoledronic acid is suspended in about 50 mL of water. The suspension is equilibrated over night at room temperature. The solid precipitate is then isolated by filtration. **With** water, T= 20 °C **Patent**; **Novartis AG**; EP1925621; (2008); (A1) English View in Reaxys



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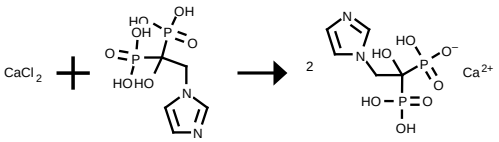
Yield	Conditions & References
	Example Name 5 Example 5: Preparation of the mutual salt of raloxifene and zoledronic acid ; 2.0 g of raloxifene was added to a mixture of 15 ml of water and 15 ml of ethanol, 1.0 g of zoledronic acid was added thereto, and the mixture was stirred at room temperature for 24 hours. The resulting mutual salt was isolated by filtration, washed with a mixture of 15 ml of water and 15 ml of ethanol, dried at 40.deg.C to obtain 2.4 g of the title compound as a cream-colored tetrahydrate. M. P. 235.deg.C Moisture content (Karl-Fisher titrator) 8.5percent (theoretical value: 8. 81percent) 'H-NMR (D20, ppm) : 5 8.62 (s, H), 7.40 (s, 1H), 7.27 (s, 1H), 7.21 (m, 3H), 7.02 (s, 1H), 6.69 (dd, 4H), 6.32 (dd, 4H), 4.59 (t, 2H), 3.95 (t, 2H), 3.24 (m, 4H), 2.72 (m, 2H). **With** ethanol, water, Time= 24h, T= 20 °C **Patent**; **HANMI PHARM. CO., LTD.**; WO2005/47282; (2005); (A1) English View in Reaxys



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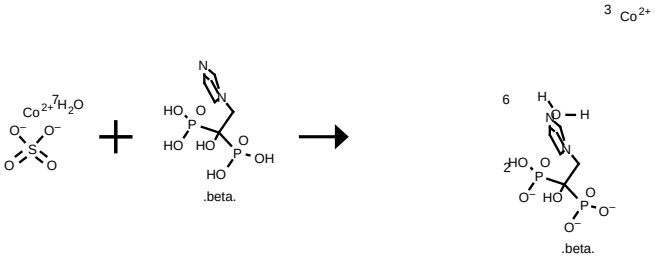
Yield	Conditions & References
	Example Name 1 Example Title Example 1 Example 1 Process for Making the Crystalline Form of the 1:2 Calcium Salt of Zoledronic acid In a 2,500 mL 3-necked flask with mechanical stirrer, 50 g zoledronic acid and 1380 mL water are added. This mixture is heated to about 90.deg.C until everything goes into solution. To this clear solution a solution of 19 g calcium chloride dihydrate in 345 mL water is added. The mixture is cooled to room temperature and stirred over night. The precipitated Ca salt is then isolated by filtration, washing with water and dried in a vacuum oven at 50.deg.C over night. This gives 49.8 g Ca salt of the following composition: C: 18.93; H: 3.82; N: 8.65; P: 20.1; Ca: 6.36; H_2O: 8.48. This corresponds to a trihydrate. m.p. >230.deg.C **in** water, T= 20 - 90 °C **Patent**; **Novartis AG**; EP1925621; (2008); (A1) English View in Reaxys



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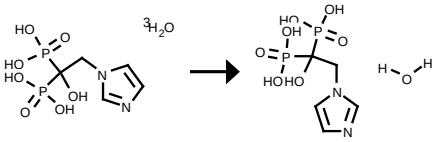
Yield	Conditions & References
75.6 %	**With** NaOH **in** water, High Pressure; a mixt. of ligand and Co salt in H2O adjusted to pH 3.48-4.45 with NaOH soln., kept in an autoclave at 180.deg.C for 5 d; cooled to room temp.; elem. anal. **Cao, Deng-Ke; Liu, Mei-Juan; Huang, Jian; Bao, Song-Song; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 50; (2011); p. 2278 - 2287 ; (from Gmelin) View in Reaxys



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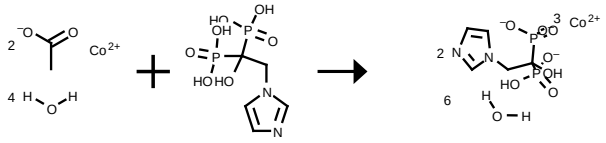
Yield	Conditions & References
	Example Name 2 EXAMPLE 2 Conversion of Trihydrate to Monohydrate by Drying 1 g of zoledronic acid trihydrate was taken in a clean Petri dish. The compound was then dried in a vacuum oven at 60.deg. C. under a vacuum of 600 mm Hg for 16 hours to obtain zoledronic acid monohydrate. , Time= 16h, T= 60 °C , p= 600Torr , Product distribution / selectivity

	Patent; **Mohakhud, Pradeep Kumar; Murki, Veerender; Nandanmudi, Kishore Babu; Babu, Moses; Banerjee, Surajit**; US2006/178439; (2006); (A1) English View in Reaxys
	Example Name 5 30 ml of water was placed into a round bottom flask along with 1 g of zoledronic acid trihydrate. The mixture was stirred for about 10 minutes at 28.deg. C. followed by heating to 99.deg. C. and was maintained at 99.deg. C. for another 30 minutes. The mixture was then allowed to cool by radiation to 57.deg. C. At this temperature, 10 ml of acetone was added to precipitate the product. The mixture was then stirred until it had cooled to 28.deg. C. The mass was maintained at 28.deg. C. for 3 hours. The separated solid was then filtered under a vacuum of 600 mm Hg. The solid was suction dried for 45 minutes and finally dried under vacuum of 600 mm Hg at 60.deg. C. for about 3 hours to afford the crystalline monohydrate of zoledronic acid. **in** water, acetone, Time= 3.66667h, T= 28 - 99 °C , Product distribution / selectivity **Patent**; **Mohakhud, Pradeep Kumar; Murki, Veerender; Nandanmudi, Kishore Babu; Babu, Moses; Banerjee, Surajit**; US2006/178439; (2006); (A1) English View in Reaxys
	Example Name 4 EXAMPLE 4 Conversion of Trihydrate to Monohydrate Using Solvent-Antisolvent Technique 30 ml of water was placed into a round bottomed flask along with 1 g of zoledronic acid trihydrate. The mixture was stirred for about 10 to 20 minutes at 28.deg. C. followed by heating to 99.deg. C. and was maintained at 99.deg. C. for another 15 minutes. The mass was then allowed to cool by radiation to 67.deg. C. At this temperature 10 ml of methanol was added to precipitate the product, and the mass was then stirred until it had cooled to 28.deg. C. The separated solid was filtered under vacuum and was washed with 10 ml of water. The solid was than suction dried under a vacuum of 600 mm Hg for 30 minutes at 28.deg. C. and finally dried at 59.deg. C. under a vacuum of 600 mm Hg for 12 hours to afford the crystalline monohydrate of zoledronic acid. **in** methanol, water, Time= 0.416667 - 0.583333h, T= 28 - 99 °C , Product distribution / selectivity **Patent**; **Mohakhud, Pradeep Kumar; Murki, Veerender; Nandanmudi, Kishore Babu; Babu, Moses; Banerjee, Surajit**; US2006/178439; (2006); (A1) English View in Reaxys
	Example Name 3 5 ml of acetone was placed into a round bottom flask along with 0.5 g of zoledronic acid trihydrate. The mixture was then stirred at 28.deg. C. for 30 minutes. The mixture was filtered under a vacuum of 600 mm Hg and the solid was finally dried under vacuum at 28.deg. C. to give the monohydrate of zoledronic acid. **in** acetone, Time= 0.5h, T= 28 °C , Product distribution / selectivity **Patent**; **Mohakhud, Pradeep Kumar; Murki, Veerender; Nandanmudi, Kishore Babu; Babu, Moses; Banerjee, Surajit**; US2006/178439; (2006); (A1) English View in Reaxys
	Example Name 2 EXAMPLE 2; CONVERSION OF MIXTURE OF TRIHYDRATE AND MONOHYDRATE TO MONOHYDRATE BY DRY-ING 1 g of zoledronic acid trihydrate was taken in a clean Petri dish. The compound was then dried in a vacuum oven at 60.deg. C under a vacuum of 600 mm Hg for 16 hours to obtain zoledronic acid monohydrate. , Time= 16h, T= 60 °C , p= 600Torr , drying in a vacuum, Product distribution / selectivity **Patent**; **DR. REDDY'S LABORATORIES LTD.; DR. REDDY'S LABORATORIES, INC.**; WO2007/32808; (2007); (A1) English View in Reaxys
	Example Name 4 EXAMPLE 4; CONVERSION OF TRIHYDRATE TO MONOHYDRATE USING SOLVENT- ANTISOLVENT TECHNI-QUE30 ml of water was placed into a round bottomed flask along with 1g of zoledronic acid trihydrate The mixture was stirred for about 10 to 20 minutes at EPO <DP n="17"/>28.deg. C followed by heating to 99.deg. C and was maintained at 99.deg. C for another 15 minutes. The mass was then allowed to cool by radiation to 67.deg. C. At this temperature

	10 ml of methanol was added to precipitate the product, and the mass was then stirred until it had cooled to 28.deg. C. The separated solid was filtered under vacuum and was washed with 10 ml of water. The solid was than suction dried under a vacuum of 600 mm Hg for 30 minutes at 28.deg. C and finally dried at 59.deg. C under a vacuum of 600 mm Hg for 12 hours to afford the crystalline monohydrate of zoledronic acid. **Stage 1: in** water, Time= 0.416667 - 0.583333h, T= 28 - 99 °C **Stage 2: in** methanol, T= 28 - 67 °C , Product distribution / selectivity **Patent**; **DR. REDDY'S LABORATORIES LTD.; DR. REDDY'S LABORATORIES, INC.**; WO2007/32808; (2007); (A1) English View in Reaxys
	Example Name 5 EXAMPLE 5; CONVERSION OF TRIHYDRATE TO MONOHYDRATE USING SOLVENT- ANTISOLVENT TECHNI-QUE30 ml of water was placed into a round bottom flask along with 1 g of zoledronic acid trihydrate The mixture was stirred for about 10 minutes at 28.deg. C followed by heating to 99.deg. C and was maintained at 99.deg. C for another 30 minutes. The mixture was then allowed to cool by radiation to 57.deg. C. At this temperature, 10 ml of acetone was added to precipitate the product. The mixture was then stirred until it had cooled to 28.deg. C. The mass was maintained at 28.deg. C for 3 hours. The separated solid was then filtered under a vacuum of 600 mm Hg. The solid was suction dried for 45 minutes and finally dried under vacuum of 600 mm Hg at 60.deg. C for about 3 hours to afford the crystalline monohydrate of zoledronic acid. **Stage 1: in** water, Time= 0.666667h, T= 28 - 99 °C **Stage 2: in** acetone, Time= 3h, T= 28 - 57 °C , Product distribution / selectivity **Patent**; **DR. REDDY'S LABORATORIES LTD.; DR. REDDY'S LABORATORIES, INC.**; WO2007/32808; (2007); (A1) English View in Reaxys
	Example Name 3 EXAMPLE 3; CONVERSION OF A MIXTURE OF MONOHYDRATE AND TRIHYDRATE TQ MONOHYDRATE BY SLURRYING5 ml of acetone was placed into a round bottom flask along with 0.5 g of zoledronic acid trihydrate. The mixture was then stirred at 28.deg. C for 30 minutes. The mixture was filtered under a vacuum of 600 mm Hg and the solid was finally dried under vacuum at 28.deg. C to give the monohydrate of zoledronic acid. **in** acetone, Time= 0.5h, T= 28 °C , Product distribution / selectivity **Patent**; **DR. REDDY'S LABORATORIES LTD.; DR. REDDY'S LABORATORIES, INC.**; WO2007/32808; (2007); (A1) English View in Reaxys



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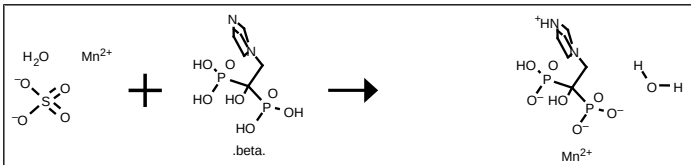
Yield	Conditions & References
56 %	**With** sodium hydroxide **in** water, High Pressure; a mixt. of a ligand (0.10 mmol) and Co-contg. compd. (0.10 mmol) in H2O (pH = 4.49, 1 M NaOH) was kept in a Teflon-lined autoclave at 160.deg.C for 48 h; after slow cooling to room temp., crystals were collected; elem. anal.; powder XRD **Cao, Deng-Ke; Li, Yi-Zhi; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 46; (2007); p. 7571 - 7578 ; (from Gmelin) View in Reaxys

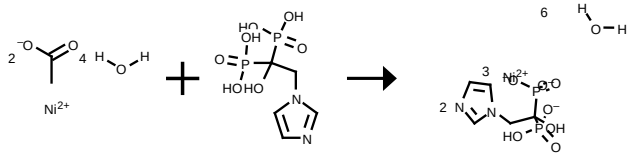


Rx-ID: 30855673 View in Reaxys

Yield	Conditions & References
64.1 %	**With** NaOH **in** water, High Pressure; a mixt. of ligand and Mn salt in H2O adjusted to pH 2.75-3.45 with NaOH soln., kept in an autoclave at 180.deg.C for 5 d; cooled slowly to room temp.; elem. anal. **Cao, Deng-Ke; Liu, Mei-Juan; Huang, Jian; Bao, Song-Song; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 50; (2011); p. 2278 - 2287 ; (from Gmelin) View in Reaxys

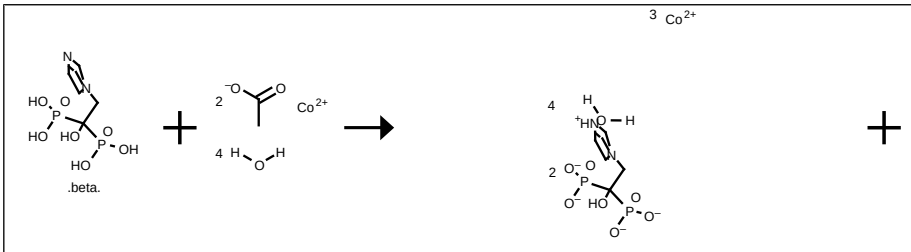
Rx-ID: 24877242 View in Reaxys

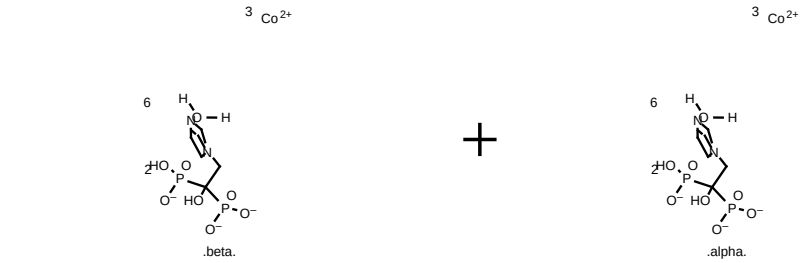
Yield	Conditions & References
	Example Name 21 Example Title EXAMPLE 21 EXAMPLE 21 A solution of 0.121 g of tris(hydroxymethyl)methylamine in 2 ml of water is added to a solution of 0.141 g of 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonic acid in 1 ml of water. The resulting solution is concentrated by evaporation in vacuo and triturated with 6 ml of warm methanol. After cooling, a cristalline precipitate is formed which is filtered off and dried for 1 hour in vacuo at 80.deg. yielding pure mono-tris(hydroxymethyl)methylammonium 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonate of m.p. 170.deg.-175.deg.. **in** methanol, water **Patent**; **Ciba-Geigy Corporation**; US4939130; (1990); (A1) English View in Reaxys



Rx-ID: 27696785 View in Reaxys

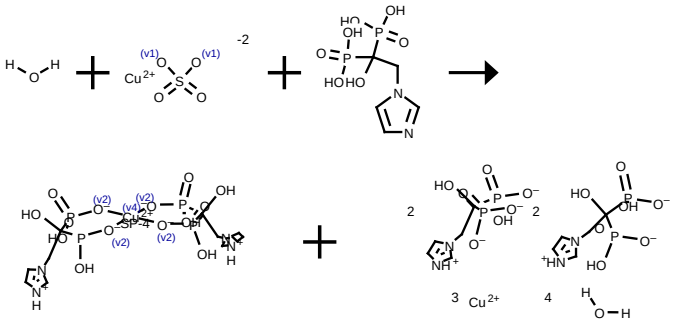
Yield	Conditions & References
54 %	**With** sodium hydroxide **in** water, High Pressure; a mixt. of a ligand (0.10 mmol) and Ni-contg. compd. (0.10 mmol) in H2O (pH = 4.50, 1 M NaOH) was kept in a Teflon-lined autoclave at 160.deg.C for 48 h; after slow cooling to room temp., crystals were collected; elem. anal.; powder XRD **Cao, Deng-Ke; Li, Yi-Zhi; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 46; (2007); p. 7571 - 7578 ; (from Gmelin) View in Reaxys





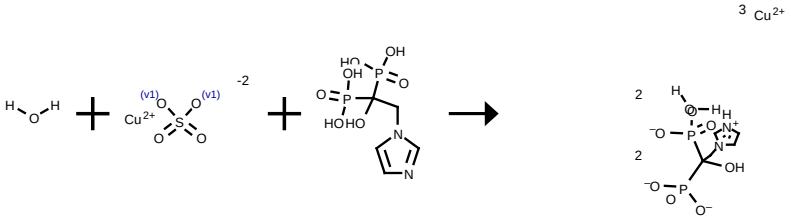
Rx-ID: 30855676 View in Reaxys

Yield	Conditions & References
50 %	**With** 4,4'-bipyridine*2H$_2$O **in** water, High Pressure; a mixt. of ligand, Co salt, 4,4'-bipyridine*2H2O and H2O kept in an autoclave for 5 h at room temp. and at 180.deg.C for 5 d; cooled to room temp., sepd. manually; elem. anal. **Cao, Deng-Ke; Liu, Mei-Juan; Huang, Jian; Bao, Song-Song; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 50; (2011); p. 2278 - 2287 ; (from Gmelin) View in Reaxys



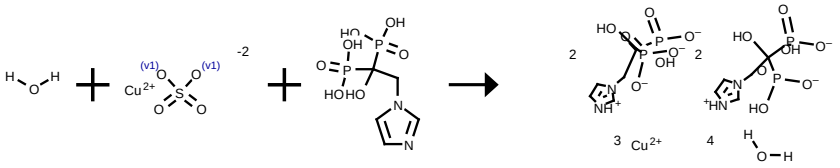
Rx-ID: 28076269 View in Reaxys

Yield	Conditions & References
29.7 %	**With** hydrogenchloride **in** water, High Pressure; a mixt. of a ligand (0.10 mmol), CuSO4 (0.05 mmol) in H2O (pH=1.5-1.6, HCl) was kept in a Teflon-lined autoclave at 120.deg.C for 24 h; slow cooling to room temp.; elem. anal. **Cao, Deng-Ke; Xie, Xiao-Ji; Li, Yi-Zhi; Zheng, Li-Min**; Dalton Transactions; (2008); p. 5008 - 5015 ; (from Gmelin) View in Reaxys
	in water, High Pressure; a mixt. of a ligand (0.10 mmol) and CuSO4 (0.05 mmol) in H2O was reactedfor 24 h at 90.deg.C and then at 120.deg.C for 24 h; elem. anal. **Cao, Deng-Ke; Xie, Xiao-Ji; Li, Yi-Zhi; Zheng, Li-Min**; Dalton Transactions; (2008); p. 5008 - 5015 ; (from Gmelin) View in Reaxys



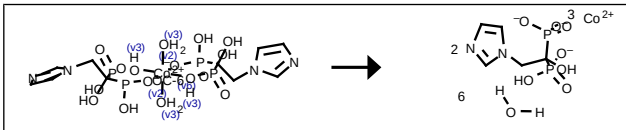
Rx-ID: 28076270 View in Reaxys

Yield	Conditions & References
70.6 %	**in** water, High Pressure; hydrothermal treatment of a mixt. of a ligand (0.10 mmol), CuSO4 (0.15 mmol) in H2O (pH=2.14) at 140.deg.C for 24 h; elem. anal.; powder XRD **Cao, Deng-Ke; Xie, Xiao-Ji; Li, Yi-Zhi; Zheng, Li-Min**; Dalton Transactions; (2008); p. 5008 - 5015 ; (from Gmelin) View in Reaxys



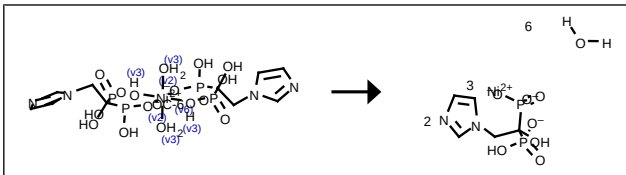
Rx-ID: 28076272 View in Reaxys

Yield	Conditions & References
50.5 %	**in** water, High Pressure; hydrothermal treatment of a mixt. of a ligand (0.10 mmol), CuSO4 (0.075 mmol) in H2O (pH=2.15) in a Teflon-lined autoclave at 120.deg.C for 24 h; elem. anal.; powder XRD **Cao, Deng-Ke; Xie, Xiao-Ji; Li, Yi-Zhi; Zheng, Li-Min**; Dalton Transactions; (2008); p. 5008 - 5015 ; (from Gmelin) View in Reaxys
	in water, High Pressure; a mixt. of a ligand (0.10 mmol) and CuSO4 (0.05 mmol) in H2O was reactedfor 24 h at 90.deg.C and then at 120.deg.C for 24 h; addnl. CuSO4 (0.1 mmol) was added; heating for 24 h at 140.deg.C **Cao, Deng-Ke; Xie, Xiao-Ji; Li, Yi-Zhi; Zheng, Li-Min**; Dalton Transactions; (2008); p. 5008 - 5015 ; (from Gmelin) View in Reaxys



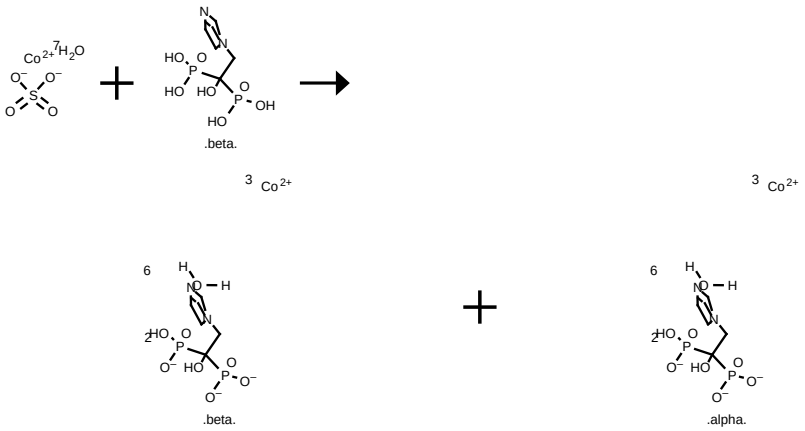
Rx-ID: 27726580 View in Reaxys

Yield	Conditions & References
0 %	**in** not given **Cao, Deng-Ke; Li, Yi-Zhi; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 46; (2007); p. 7571 - 7578 ; (from Gmelin) View in Reaxys



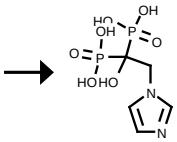
Rx-ID: 27726581 View in Reaxys

Yield	Conditions & References
0 %	**in** not given **Cao, Deng-Ke; Li, Yi-Zhi; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 46; (2007); p. 7571 - 7578 ; (from Gmelin) View in Reaxys



Rx-ID: 30855675 View in Reaxys

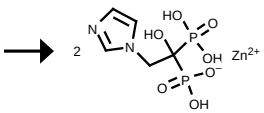
Yield	Conditions & References
	in water, High Pressure; adjusted to pH 3.03-3.48, kept in an autoclave at 180.deg.C for 5 d; obtained as a mixt. **Cao, Deng-Ke; Liu, Mei-Juan; Huang, Jian; Bao, Song-Song; Zheng, Li-Min**; Inorganic Chemistry; **vol.** 50; (2011); p. 2278 - 2287 ; (from Gmelin) View in Reaxys



Rx-ID: 23426874 View in Reaxys

Yield	Conditions & References
98.7 %	Example Name 5 Example 5:Recrystallization of Zoledronic Acid Monohydrate:[0024] A jacketed 3 liter flask, fitted with a stirrer, thermocouple and nitrogen adapter was charged with water (1.5 1) and 64.4 g of crude zoledronic acid monohydrate. The aqueous mixture was heated to 85.deg.C and all solids dissolved giving a pH of 1.7. Absolute ethanol (500 ml) and zoledronic acid monohydrate seeds were added to the aqueous mixture creating a slurry, which was slowly cooled with stirring. At 38.deg.C, the pH was adjusted from 3.7 to 1.7 with hydrochloric acid. At 18^0C, the aqueous mixture was adjusted to pH greater than 2. The slurry was stirred at O^0C for about 4 hours then the solid was filtered, washed with ethanol (2 x 200 ml) and dried with nitrogen yielding 58.64 g of zoledronic acid monohydrate. The product was dried further in a vacuum drying oven at $5O^0$C, 1-2 in. nitrogen, giving a loss of 0.28 wtpercent. An NMR assay indicated a product purity of 92.2 wt percent (on an anhydrous basis). Karl-Fischer titration indicated 6.46percent water corresponding to 98.7 percent zoledronic acid hydrate with the water to a zoledronic mole ratio of 1.06:1. ^{1}H NMR (D2O/NaOD): 7.75 (s, IH); 7.23 (s, IH); 6.90 (s, IH); 4.82 (O-H, 7.35H); 4.46 (m, 2H); ^{31}P (H coupled, D2O/NaOD): 16.83 (m). **With** hydrogenchloride **in** ethanol, water, T= 0 - 85 °C , pH= 1.7 - 3.7, Purification / work up **Patent**; **ALBEMARLE CORPORATION**; WO2007/109542; (2007); (A2) English View in Reaxys
62 %	Example Name 2 **Patent**; **LYOGEN LIMITED**; WO2005/63779; (2005); (A2) English View in Reaxys
	Examples of particularly preferred N-bisphophonates for use in the invention are: ... 1- Amino-2-(1-methylimidazol-4-yl)ethane-1,1-diphosphonic acid; 1- Amino-2-(1-benzylimidazol-4-yl)ethane-1,1-diphosphonic acid; 2-(1-Methylimidazol-2-yl)ethane-1,1-diphosphonic acid; 2-(1-Benzylimidazol-2-yl)ethane-1,1-diphosphonic acid; 2-(Imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid; 2-(Imidazol-1-yl)ethane-1,1-diphosphonic acid; 2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid; 2-(Thiazol-2-yl)ethane-1,1-diphosphonic acid; ... **Patent**; **Horowitz, Zebulun D.; Richardson, Peter C.; Trechsel, Ulrich**; US2003/181421; (2003); (A1) English View in Reaxys
	The oral dosage form according to claim 6, wherein the bisphosphonate is selected from the group consisting of: ... 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate); 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid(risedronate); 1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate); 1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid; 1-hydroxy-2-(1-imidazolyl)etylidene-1,1-bisphosphonic acid (zoledronate); 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid (minodronate); 1-(4-chlorophenylthio)methylidene-1,1-bisphosphonic acid (tiludronate); 1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate); and

	... **Patent**; **AstraZeneca AB**; US6372728; (2002); (B1) English View in Reaxys
	Example Name 10 Example Title EXAMPLE 10 EXAMPLE 10 With stirring and under reflux, 8.6 g (0.053 mole) of imidazol-1-ylacetic acid hydrochloride, 7.1 ml of 85percent phosphoric acid and 25 ml of chlorobenzene are heated to 100.deg. C. Then 13.9 ml of phosphorus trichloride are added dropwise at 100.deg. C., whereupon evolution of gas occurs. Over the course of 30 minutes a dense mass precipitates from the reaction mixture. The batch is heated for 3 hours to 100.deg. C. and the supernatant chlorobenzene is removed by decantation. The residual viscous mass is heated for 3 hours to the boil, with stirring and under reflux, with 40 ml of 9N hydrochloric acid. The batch is then filtered hot with the addition of carbon and the filtrate is diluted with acetone, whereupon the crude 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid precipitates. This product is recrystallized from water. Melting point: 239.deg. C. (dec.). Yield: 41percent of theory. **Patent**; **Ciba-Geigy Corporation**; US4939130; (1990); (A1) English View in Reaxys
	the bisphosphonates are selected from the group which comprises aminohydroxymethylidene bisphosphonic acids, ... 3-methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonic acid, 2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid, 1-hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bisphosphonic acid, cycloheptylaminomethylene diphosphonic acid, **Patent**; **BioAgency AG**; EP1140113; (2003); (B1) German View in Reaxys
	Examples of particularly preferred bisphophonates for use in the invention are: ... 1-Amino-2-(1-methylimidazol-4-yl)ethane-1,1-diphosphonic acid; 1-Amino-2-(1-benzylimidazol-4-yl)ethane-1,1-diphosphonic acid; 2-(1-Methylimidazol-2-yl)ethane-1,1-diphosphonic acid; 2-(1-Benzylimidazol-2-yl)ethane-1,1-diphosphonic acid; 2-(Imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid; 2-(Imidazol-1-yl)ethane-1,1-diphosphonic acid; 2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid; 2-(Thiazol-2-yl)ethane-1,1-diphosphonic acid; ... **Patent**; **Fox, Alyson; Green, Jonathan; O'Reilly, Terence; Urban, Laszlo; Walker, Katharine**; US2004/63670; (2004); (A1) English View in Reaxys



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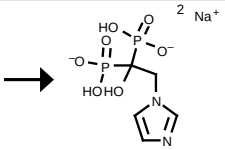
Yield	Conditions & References
	Example Name 3 By stirring 46.3 g of this product in 2 L ethanol:water 1:1 over night, filtration and drying in a vacuum oven at 50.deg.C over night 46.9 g of a single modification is obtained. This product has the following composition: C: 18.01; H: 3.62; N: 8.20; P: 19.1; Zn: 10.5 and H_2O: 8.08. **in** ethanol, water, Purification / work up

	Patent; **Novartis AG**; EP1925621; (2008); (A1) English View in Reaxys



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Yield	Conditions & References
	Patent; **MUSTAFA NEVZAT ILAC SANAYII A.S.**; WO2005/54260; (2005); (A1) English View in Reaxys