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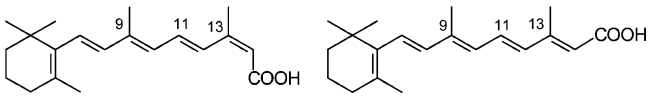
An Efficient Commercial Process for the Preparation of Isotretinoin†

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Abstract:
We describe an efficient process for the preparation of isotretinoin (13-cis isomer of vitamin A acid) in a single step starting from β-ionylidene acetaldehyde (5). The process conditions are convenient to operate on a commercial scale and afford isotretinoin of excellent quality; levels of related isomeric impurities such as tretinoin (all trans retinoic acid) and 9,13-di-*cis*-retinoic acid are extremely low. Thus, condensation of dienolate of methyl 3,3-dimethylacrylate with β-ionylidene acetaldehyde (5) followed by aqueous acidic workup afforded isotretinoin in >95% purity. The condensation reaction proceeds via in situ formation of lactone (8); furthermore, the reaction conditions have been optimized to exploit in situ generated methoxide anion for lactone ring opening to afford the desired product. Distinct advantages of this process are that it does not require isolation of intermediate lactone and utilizes in situ generated methoxide for lactone ring opening, thus obviating the need for an additional step and base. We also describe an optimized process for the preparation of β-ionylidene acetaldehyde (5), a key intermediate for isotretinoin.

Introduction

Isotretinoin (13-*cis*-retinoic acid) belongs to a family of vitamin A (retinol) related compounds. It inhibits sebaceous gland function and keratinization and is used for the treatment of dermatological diseases such as acne. It is extremely effective in very severe and nodulocystic acne and prevents scarring. Isotretinoin has also been evaluated for its potential use in certain cancerous conditions.[1]

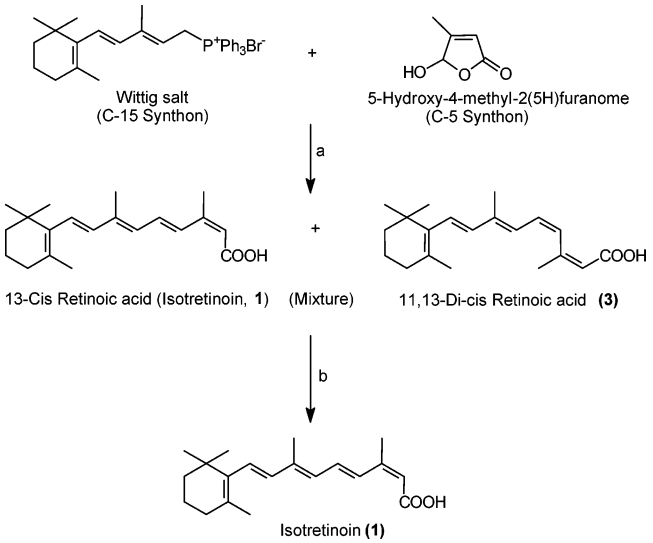


Isotretinoin **(1)** Tretinoin **(2)**

Structurally, isotretinoin is a highly conjugated molecule consisting of a substituted cyclohexene moiety and a polyene side chain with a terminal carboxy group. All except one of the double bonds (C-13 double bond) in the side chain are trans, and it is the stereospecific construction of this polyene side chain that has challenged synthetic organic chemists for the past almost three decades. Commercially and readily available β-ionone (**4**) has been conveniently used for the construction of the cyclohexene part of isotretinoin.

Reported synthetic approaches[2−7] for the construction of the polyene side chain do not offer a commercially viable process. In general, the approach has been to develop a convergent synthesis involving stereospecific coupling of an appropriate C_{15} synthon (synthesized from β-ionone) and a C_5 synthon. For example, Pattenden and Weedon[3] utilized the reaction of C_{15}-triarylphosphonium salt (Wittig salt) with a C_5-butenolide in diethyl ether. This process however gave an isomeric mixture (at the C-11 double bond) of 13-cis retinoic acid in 66.75% yield; the desired 11-trans-13-cis content was only about 36% and the rest being the corresponding 11,13-di-cis isomer (Scheme 1).

Scheme 1[a]



[a] Reagents: (a) base/protic/aprotic solvent; (b) *hν*/iodine or *hν*/Pd-salt or hν/photosensitizer.

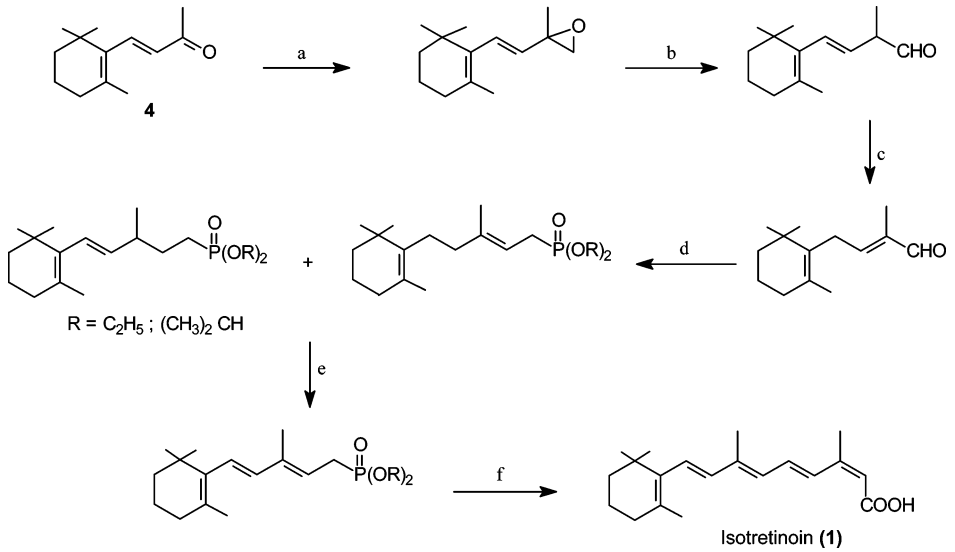
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† Portions of this work have been incorporated in the following patent/patent applications: U.S. 6,441,226B1 and WO 2003018522 A2.

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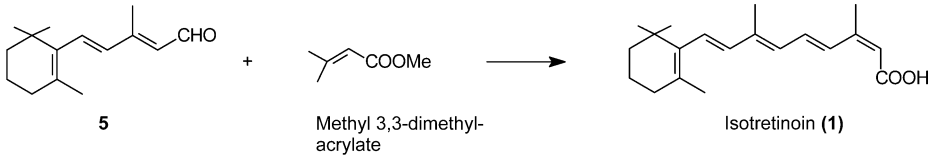
Published on Web 03/03/2005
10.1021/op0497815 CCC: $30.25 © 2005 American Chemical Society

Scheme 2[a]



[a] Reagents: (a) (i) trimethylsulfoxonium iodide, NaH/DMSO, (ii) DMSO/THF, −5 °C; (b) $MgBr_2$; (c) isomerization; (d) tetraethyl/tetraisopropyl methylenedisphosphonate, base; (e) alkoxide, DMSO; (f) 5-hydroxy-4-methyl-2(5H)furanone, KO-*tert*-butoxide, THF/DMSO.

Scheme 3[a]



[a] Reagents: (i) NaNH2, liq ammonia, ether, −30 °C, 72 h, (ii) KOH, (iii) H^+/H_2O.

Selective isomerization of the 11-cis double bond in the presence of the 13-cis double bond proved extremely difficult to accomplish. Some of the methods attempted include photoisomerization using iodine,[4] transition metal catalyst,[5] or photosensitizers such as Erythrosin B or Rose Bengal,[6] etc.

The above synthetic approach to prepare isotretinoin is not amenable for commercial scale; limitations include the need for special equipment for photoisomerization and suboptimal purity of the desired product.

James Babler[8] has described use of phosphonate ester (as C_{15} synthon) as the key intermediate for the synthesis of isotretinoin (Scheme 2); the phosphonate ester in turn was synthesized in several steps from β-ionone. Condensation of the phosphonate ester with 5-hydroxy-4-methyl-2(5*H*)-furanone (C-5 synthon) afforded isotretinoin. Although this approach does not involve the cumbersome photoisomerization step, it is uneconomical for commercial manufacturing because of the number of the steps involved.

A patent report[9] has described preparation of isotretinoin in a single step from β-ionylidene acetaldehyde (**5**) and methyl 3,3-dimethylacrylate in the presence of sodium amide and liquid ammonia. However, these reaction conditions require maintaining low temperatures for more than 22 h (Scheme 3) making this process suboptimal for commercial scale synthesis. The patent report also does not indicate the impurity profile of isotretinoin obtained through this process.

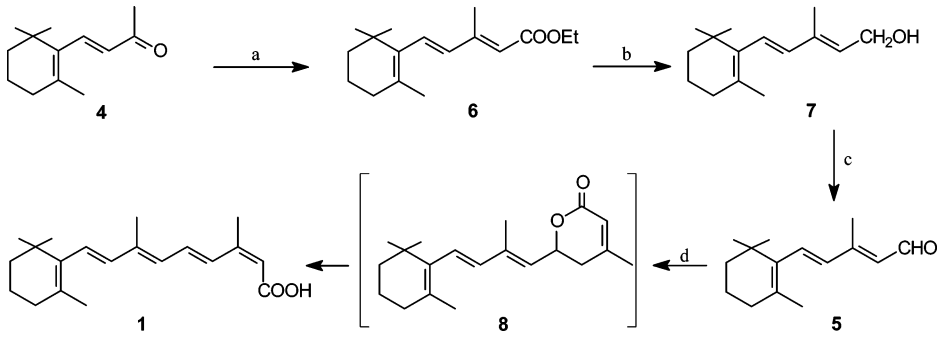
Results and Discussion

A more practical approach to isotretinoin synthesis has been reported by Cainelli et al.[10] involving conversion of lactone (**8**) to isotretinoin in the presence of KO-*tert*-butoxide. These authors however described a rather difficult route to the lactone (**8**) intermediate. A later report by Dugger and Heathcock[11] described a more efficient synthesis of the key lactone intermediate (**8**); condensation of dienolate of methyl 3,3-dimethyl acrylate (generated from LDA and methyl 3,3-dimethyl acrylate) with β-ionylidene acetaldehyde (**5**) at −78 °C afforded the desired lactone (**8**) after preparative HPLC purification. These two reports in fact form the basis of our present study. We argued that it should be possible to optimize the reaction conditions in Dugger and Heathcock's process to obtain isotretinoin in one single step. Mechanistically, condensation of dienolate of methyl 3,3-dimethyl acrylate with β-ionylidene acetaldehyde (**5**) would result in the generation of methoxide anion, and we argued that it should be possible to utilize this in situ generated base to affect lactone ring opening and obtain isotretinoin. The novelty of this process would be that it would not require isolation of lactone intermediate and more importantly would not require use of additional base (such as KO-*tert*-butoxide, as used by Cainelli et al.[10]).

Indeed, condensation of dienolate of methyl 3,3-dimethyl acrylate with β-ionylidene acetaldehyde (**5**), first at −78 °C and subsequently at 40 °C (to affect ring opening), afforded,

(8) Babler, J. H. U.S. Patent 4,916,250, 1990.
(9) Johnson, J. Y.; Johnson, G. W. GB Patent 835,526, 1958.
(10) Cainelli, G.; Cardillo, G.; Contento, M.; Grasselli, P.; Umani-Ronchi, A. *Gazz. Chim. Ital.* **1973**, *103*, 117.
(11) Dugger, R. W.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1181.

Scheme 4[a]



[a] Reagents: (a) triethyl phosphonoacetate, $NaNH_2$, toluene, 65 °C, 15 h; (b) (i) LAH, THF−hexane, (ii) H^+/H_2O; (c) MnO_2, hexane, 60 °C, 3 h; (d) (i) LDA, methyl 3,3-dimethyl acrylate, −72 °C, 1 h, (ii) 40 °C, 1 h, (iii) H^+/H_2O.

after aqueous acid workup, isotretinoin in a single step (Scheme 4). The process does not require any chromatographic purification step, and simple recrystallisation affords the desired isotretinoin in good yield and excellent purity. This process has also been successfully used at the commercial scale for the production of isotretinoin.

We also describe an optimized process for the preparation of key intermediate, β-ionylidene acetaldehyde (**5**).

Thus, condensation of β-ionone (**4**) with triethyl phosphonoacetate in toluene in the presence of sodium amide afforded ethyl β-ionylidene acetate (**6**) in 85% isolated yield and >95% purity. Reduction of ester **6** with lithium aluminum hydride in a mixture of hexanes and anhydrous THF gave the corresponding alcohol, β-ionylidene ethanol (**7**); this was used as such for the oxidation step. Oxidation of **7** with activated manganese dioxide in hexanes at 60 °C afforded the desired *trans*-β-ionylidene acetaldehyde (**5**, containing less than 5% of the corresponding 9-cis isomer) in 95% yield over two steps.

Conclusions

We have successfully developed an efficient commercial process for the synthesis of isotretinoin (**1**) and also report an optimized process for the preparation of key intermediate, β-ionylidene acetaldehyde (**5**). The reaction conditions are operationally simple, robust, and amenable to commercial scale synthesis.

Experimental Section

General. Starting materials were obtained from commercial suppliers and used without further purification. Gas chromatography was performed with HP 50 (30 mm × 0.53 mm column, fused silica coated with dimethylpolysiloxane as stationary phase, 2.65 μm film thickness). HPLC was performed with a Waters' instrument (version 3.05.01) using a Kromosil C-18 column (5μ, 250 mm × 4.6 mm). ^{1}H NMR spectra were recorded in $CDCl_3$ using a Bruker 300 MHz. The chemical shift data are reported as δ (ppm) downfield from tetramethylsilane which was used as an internal standard.

Preparation of Ethyl β-Ionylidene Acetate (6). Under nitrogen and with stirring, a solution of triethyl phosphonoacetate (1.4 kg, 6.25 mol) in toluene (1 L) was added to a mixture of sodium amide (236 g, 6.05 mol) and toluene (6.5 L) at about 40 °C. The reaction mixture was stirred at 40−45 °C for 6 h and cooled to 0−5 °C, and a solution of β-ionone (1 kg, 5.2 mol) in toluene (1.5 L) was slowly added at 0 to 10 °C. The reaction mixture was stirred at 65 °C, and progress was monitored by GC. After the completion of the reaction (β-ionone less than 5% by GC, approximately 15 h), the mixture was cooled to 20−25 °C, washed with water (2 × 4 L), and concentrated under vacuum. Distillation under reduced pressure (2−3 mm) afforded the desired ethyl β-ionylidene acetate (**6**) in >95% purity (by GC); yield 1.16 kg (85%); bp 145−150 °C at 2.5 mm; ^{1}H NMR δ 1.01 (s, 6H, 2 × CH_3), 1.27 (t, 3H, −OCH$_2$CH_3, J = 3.2 Hz), 1.47 (m, 2H, ring-CH_2), 1.59 (m, 2H, ring-CH_2), 1.68 (s, 3H, CH_3), 2.02 (m, 2H, ring-CH_2), 2.33 (s, 3H, CH_3), 4.15 (q, 2H, −OCH_2, J = 7.08 Hz), 5.73 (s, 1H, =CH), 6.08 (d, 1H, =CH, J = 16 Hz) and 6.54 (d, 1H, =CH, J = 16 Hz).

Preparation of β-Ionylidene Acetaldehyde (5). Under nitrogen and with stirring, lithium aluminum hydride (110 g, 2.89 mol) was added to a mixture of hexanes (9.5 L) and anhydrous THF (1 L). A solution of ethyl β-ionylidene acetate (**6**, 1 kg, 3.82 mol) in THF (2 L) was added slowly at 30−35 °C. The reaction mixture was stirred for 1 h at 30−35 °C and cooled to 0−2 °C. Aqueous sulfuric acid (0.9 L) was then added very slowly at 0−10 °C. The solids were removed through filtration and washed with hexanes (3.5 L). The combined filtrate containing the desired β-ionylidene ethanol (**7**) was used as such for the subsequent oxidation step, as follows.

Under stirring, manganese dioxide (3 kg, 34.5 mol) was added to the filtrate containing β-ionylidene ethanol (**7**) obtained in the previous step at room temperature. The reaction mixture was refluxed at 60 °C for 3 h and filtered. The solids were washed with hexanes (6 L), and the combined filtrate layer was concentrated under vacuum to yield the desired β-ionylidene acetaldehyde (**5**); yield 0.80 kg (95.3% over two steps); 9-cis isomer (less than 5% by HPLC); ^{1}H NMR δ 1.07 (s, 6H, 2 × CH_3), 1.48−1.51 (m, 2H, ring-CH_2), 1.63−1.66 (m, 2H, ring-CH_2), 1.74 (s, 3H, CH_3), 2.06−2.14 (m, 2H, ring-CH_2), 2.33 (s, 3H, CH_3), 5.95 (d, 1H, =CH, J = 8.1 Hz), 6.23 (d, 1H, =CH, J = 16.2 Hz), 6.27 (d, 1H, =CH, J = 16.2 Hz), and 10.16 (d, 1H, CHO, J = 8.1 Hz).

Preparation of Isotretinoin (1). Under nitrogen and with stirring, a solution of *n*-BuLi in hexane (15%, 321 mL) was

added to a solution of diisopropylamine (48.6 g, 0.48 mol) in anhydrous THF (1 L) at −30 °C and the mixture was stirred for 1 h. The reaction mixture was then cooled to −72 °C, and methyl 3,3-dimethyl acrylate (54.8 g, 0.48 mol) was added to it. Stirring was continued at −65 to −75 °C for 30 min. A solution of β-ionylidene acetaldehyde (**5**, 100 g, 0.458 mol) in anhydrous THF (350 mL) was added, and the reaction mixture was stirred at −65 to −75 °C for 1 h, warmed to 40 °C, and stirred at this temperature for 1 h. Solvent was removed under vacuum, and the reaction mixture was diluted with water (700 mL) and methanol (300 mL). Activated charcoal (4 g) was then added, and the mixture was refluxed for 30 min. The heterogeneous mixture was filtered through Hyflo, and the Hyflo bed was washed with methanol (300 mL) and water (150 mL). The aqueous methanolic layer was then washed with hexanes (2 × 500 mL), acidified with 10% aqueous sulfuric acid to pH 3, and extracted with dichloromethane (2 × 500 mL). The combined dichloromethane layer was washed with water (2 × 300 mL) and concentrated in vacuo. Crystallization from methanol (200 mL) afforded the desired isotretinoin; yield 55 g, (40%). Recrystallization from methanol (1.375 L) afforded pure (greater than 99% by HPLC; the tretinoin content was less than 0.1%) isotretinoin; yield 44.5 g; ^{1}H NMR δ 1.03 (s, 6H, 2 × C*H*$_3$ at C-1), 1.45−1.49 (m, 2H, ring-C*H*$_2$ at C-2), 1.60−1.66 (m, 2H, ring-C*H*$_2$ at C-3), 1.72 (s, 3H, C*H*$_3$ at C-5), 2.00−2.05 (m, 5H, C*H*$_3$ at C-9 and C*H*$_2$ at C-4), 2.10 (s, 3H, C*H*$_3$ at C-13), 5.66 (s, 1H, *H*-14), 6.165 (d, 1H, *H*-8, J = 15 Hz), 6.25−6.32 (m, 2H, *H*-7 and *H*-10), 6.98−7.07 (dd, 1H, *H*-11, J = 15 Hz,), 7.745 (d, 1H, *H*-12, J = 15 Hz), and 11.25 (broad s, 1H, COO*H*, D_2O exchangeable)

Acknowledgment

We are grateful to the Analytical Division of Ranbaxy Research Laboratories for providing analytical and spectral data. The authors also wish to thank Professor U. K. Pandit for many helpful discussions.

Received for review December 3, 2004.

OP0497815