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Development of a Practical, Safe, and High-Yielding Process for the Preparation of Enantiomerically Pure *trans*-Cyclopropane Carboxylic Acid

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Abstract:

A practical, safe, and high-yielding process for the cyclopropanation of a chiral epoxide has been developed using the inexpensive and nonhazardous reagents triethylphosphonoacetate and sodium *tert*-butoxide.

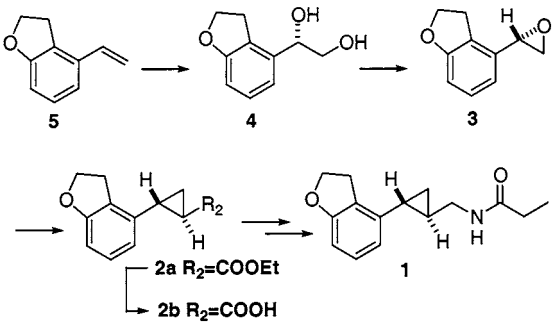
Introduction

Cyclopropane ring systems are ubiquitous in nature and are contained in a large number of natural products, insecticides, and pharmaceutical drug candidates.[1] In conjunction with our work on the melatonergic agent **1**[2] (Scheme 1), we needed to develop a cost-effective process for the large-scale preparation of the enantiomerically pure *trans*-cyclopropane carboxylic acid **2b**.

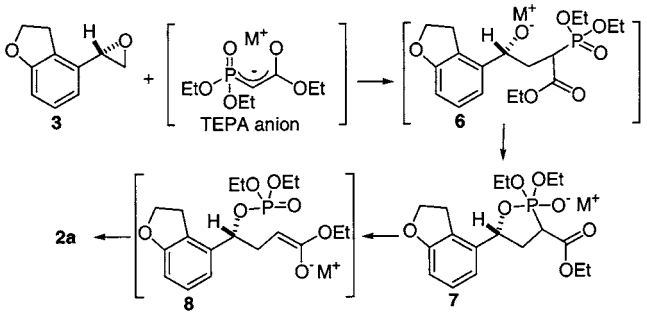
The reaction of epoxides with the anion of triethylphosphonoacetate (TEPA) in the synthesis of cyclopropane derivatives has been known for over four decades,[3] and there has been occasional additional application of the reaction between epoxides and phosphonates (either α-phosphono esters or phosphono ketones).[4] However, the utility of this reaction for the large-scale preparation of cyclopropane derivatives has not been explored. We were attracted toward developing the use of TEPA for the conversion of **3** to **2a** due to its low cost, ease of availability and handling on-scale. Most of the cited procedures use NaH as the base and afford the cyclopropane derivatives in fair yields (20−60%). Therefore, to make such a procedure scale-worthy, we needed to find a suitable substitute for NaH (dust hazard, hydrogen evolution, moisture sensitivity, etc.) and to identify reaction conditions to significantly improve the overall yield of the reaction.

Herein, we wish to report the development of a safe, practical, and high-yielding process for the conversion of **3** to **2a** by using the chemistry of TEPA anion and subsequent isolation of **2b**.

Scheme 1



Scheme 2. **Mechanism of formation of *trans*-cyclopropane derivative**



Results and Discussion

Epoxide **3**[5] having >99% ee was prepared in two steps (overall yield 85%, HPLC area percent 97) by the Sharpless asymmetric dihydroxylation of **5** using AD-mix-α to diol **4**,[6] followed by stereospecific transformation of **4** to **3** (Scheme 1).[7]

The mechanism of the cyclopropanation reaction (Scheme 2) was first discussed by Wadsworth and Emmons, where the intermediacy of a cyclic phosphonate similar to **7** was proposed.[3] Reactions conducted with epoxide **3** showed the presence of a peak by HPLC having the molecular weight

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(1) (a) Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243. (b) Nagle, D. G.; Gerwick, W. H. *Tetrahedron Lett.* **1990**, *31*, 2995.

(2) Zhu. J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett*. **2000**, *41*, 4011.

(3) (a) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733. (b) Denney, D. B.; Vill, J. J.; Boskin, M. J. *J. Am. Chem. Soc*. **1962**, *84*, 3944.

(4) (a) Tomoskozi, I. *Tetrahedron* **1963**, *22*, 1969. (b) Izydore, R. A.; Ghirardelli, R. G. *J. Org. Chem.* **1973**, *38*, 1790. (c) Jacks, T. E.; Nibbe, H.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 4584 and references therein. (d) Meul, T.; Weinhold, P.; Lonza, A. G. Eur. Pat. 491330, 1992.

(5) Epoxide **3** was also prepared by Jacobsen's asymmetric epoxidation method[a,b] and enzyme mediated selective hydrolysis of undesired enantiomer from racemic epoxide;[c] however, these methods were not suitable for scale-up: (a) Senanayake, C. H.; Jacobsen, E. N. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K., Ed.; Dekker: New York, 1999; p 347. (b) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1994**, 20, 9333. (c) Goswami, A.; Totleben, M. J.; Singh, A. K.; Patel, R. N. *Tetrahedron: Asymmetry* **1999**, 3167.

(6) (a) Ahrgren, A.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (c) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(7) Kolbe, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

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Table 1. **Effect of key reaction parameters on the in-process conversion to 2a**

entry	base	reaction solvent	temp (°C)	reaction time (h)	**2a** (% conv. by HPLC)
1	KTA	toluene	80	24	60
2	KTA	MeTHF	80	20	97
3	KTA	*tert*-amyl alcohol	100	40	90
4	KTA	THF	65	18	83
5	KTA	DME	65	18	76
6	KTA	DMF	65	18	80
7	KTA	DMSO	65	18	83
8	HexLi	MeTHF	80	20	97
9	Hex Li	DME	80	12	65
10	Hex Li	DME	65	16	76
11	EtMgCl	MeTHF	80	20	93
12	KO^{t}Bu	DME	60	18	80
13	NaO^{t}Bu	DME	60	18	80
14	KO^{t}Bu or NaO^{t}Bu	DME	60 °C for 15 h, 70 °C for 9 h		93

of intermediate **7** (M = H) as determined by LC/MS. Upon further heating, **7** was converted into **2a**, presumably via the intermediacy of the ester enolate **8**. As reported in the literature, the *trans*-product **2a** was the only product, and the *cis*-isomer could not be detected by HPLC.

To evaluate the scalability of this reaction, we systematically studied the effect of concentration, solvent, base, and temperature on the rate of reaction and the extent of reaction completion.

Effect of Concentration. Although the rate of reaction was faster at >1 M concentration of **3**, the reaction mixture turned into a very thick slurry and could not be stirred efficiently. At <1 M concentration, the reaction time was >24 h. Therefore, we selected ca. 1 M as the optimal concentration for the reaction.

Effect of Base and Solvent. Since the anion of TEPA can be formed by almost any base (hydrides, hydroxides, alkoxides, amines, and alkyllithiums), we screened several common bases in different solvents at different temperatures to find a suitable substitute for NaH. Table 1 includes results from experiments where the in-process conversion to **2a** was at least 60% by HPLC.[8] Initial experiments were carried out with potassium *tert*-amylate (KTA) because it is a very common and inexpensive base. Since KTA is commercially sold as a solution in toluene, we first evaluated toluene as the reaction solvent. Reactions conducted in toluene using KTA did not go to completion at 60 °C, and at higher temperature, the percent conversion was at best 60% (entry 1). In other solvents, the conversion was much better (entries 2−7); however, these solvents were not considered for scale-up because a solvent exchange (from toluene to the desired reaction solvent) would be required. Likewise, hexyllithium (Hex Li) or EtMgCl in 2-MeTHF were not considered for scale-up, although the percent conversion to **2a** was excellent (entries 8 and 11). Using Hex Li in 1,2-dimethoxyethane

(8) There was no product formation with triethylamine or diisopropylethylamine (DIPEA) in THF at 65 °C. About 16% product formed using DIPEA in combination with 1 equiv of LiBr and DIPEA as the reaction solvent at 100 °C.

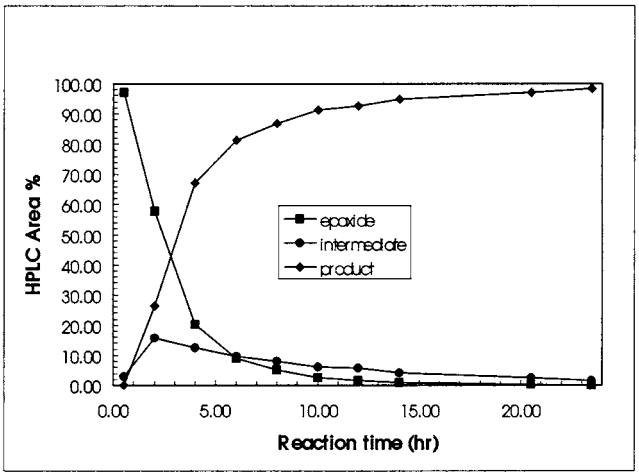

Figure 1. **In-process monitoring of cyclopropanation reaction.**

(DME[9]), the percent conversion was lower at 80 °C (entry 9) but was better at 65 °C (entry 10). Using DME as the solvent, we also evaluated KO^{t}Bu and NaO^{t}Bu. Both bases worked very well (entries 12 and 13). DME was selected as the reaction solvent because it allowed telescoping of the epoxidation and cyclopropanation steps and offered better solubility of the TEPA anion.

Effect of Temperature. The rate of reaction was considerably slow at temperatures below 50 °C. Therefore, all the reactions were conducted at 60 °C or higher. To understand the low yield of the reaction at higher temperatures, the stability of **3** and **2a** were studied at 80 °C. The epoxide **3** was stable for extended periods of time, but the product **2a** slowly degraded by 10−15% in 24 h. A careful in-process monitoring (Figure 1) of the reaction revealed that at 60 °C most of the epoxide **3** was consumed in ca. 12 h, and the reaction mixture contained about 5−10% of intermediate **7**. Once the epoxide was consumed, the temperature of the reaction could be raised to 70 °C to "burn-off" the remaining **7**. This tactic worked very well, improving the yield of the reaction to >90% (entry 14). With the improved reaction conditions in hand, NaO^{t}Bu was selected for further scale-up work due to its ease of handling, low hazards, and low cost. Additionally, the reaction mixture was less viscous due to increased solubility of sodium phosphonoacetate in DME, allowing for improved agitation.

The free acid **2b** is a low-melting solid. For the isolation of **2b**, the reaction mixture containing **2a** was hydrolyzed with NaOH, and after pH adjustment, **2b** was extracted into ethyl acetate (EtOAc). The solution of **2b** in EtOAc was suitable for the subsequent steps leading to **1**.

Summary

We have developed a practical, safe, and high-yielding process for the cyclopropanation of a chiral epoxide using the inexpensive and nonhazardous reagents TEPA and NaO^{t}Bu. The chemical yield of 85−90% is a significant improvement over examples (20−60%) reported previ-

(9) Although DME is a common solvent, appropriate protective measures must be taken when handling DME due to possible teratogenic (target organ: liver, kidneys) and reproductive hazard effects.

ously.[3,4] This was achieved through a careful study of the effects of various reaction parameters on the yield and quality of the product. Since only one diastereomer forms under the cyclopropanation reaction conditions, the diastereomeric excess of the product **2a** was the same as that of input epoxide **3** (>99% ee). This process was demonstrated on-scale, where 14 kg of **2b** was prepared as a solution in EtOAc.

Experimental Section

General. NaO^{t}Bu and TEPA are commercially available and were used as-is. DME and EtOAc were used without any further purification. DME was checked for peroxides with indicator strips prior to use. For pH measurement, a Radiometer PHM82 standard pH meter with an Omega pH electrode was used. The electrode was standardized using pH 4.0, 7.0, and 10.0 buffers. Moisture content was determined by coulometric titration on a Mitsubishi CA-06 moisture meter on a weight/volume basis. Proton and carbon NMR were run on a Bruker AC-300 spectrometer at 300 MHz for proton and 75 MHz for carbon in $CDCl_3$. HPLC was run under the following conditions: column YMC ODS-A, 150 × 6 mm i.d., S-3 μm; column temperature 30 °C; flow rate 1.0 mL/min; λ 210 nm; injection volume 10 μL; mobile phase A, 45% (v/v) 0.01 M KH_2PO_4 (pH 3) in CH_3CN; mobile phase B, 20% (v/v) 0.01M KH_2PO_4 (pH 3) in CH_3CN; gradient program 0−15 min (100% A), 15−20 min (linear gradient to 100% B), 20−25 min (linear gradient to 100% A); retention times in minutes 5.2 (**2b**), 7.0 (**3**), 9.8 (**7**), and 15.4 (**2a**). Chiral HPLC was run under the following conditions: column Chiralcel OJ-R OCD-HJ019, 4.6 × 150 mm i.d., S-5μ; column temperature ambient; flow rate 1.0 mL/min.; λ 285 nm; injection volume 10 μL; isochratic program; mobile phase 35% (v/v) water in methanol containing 0.5 mL trifluoroacetic acid per 1 L of mobile phase; retention times in minutes 6.7 (1*R*,2*S*), 7.5 (1*S*,2*R*), 10.2 (1*R*,2*R*), 12.5 (1*S*,2*S*). LC/MS was run under the following conditions: column YMC ODS-AQ, 4.6 × 150 mm; flow rate 1.0 mL/min; linear gradient from 100% mobile phase A to 100% mobile phase B over 20 min.; mobile phase A, 90% (v/v) 0.01 M NH_4OAc in acetonitrile; mobile phase B, 10% (v/v) 0.01 M NH_4OAc in acetonitrile.

Preparation of 2b. NaO^{t}Bu (5.93 g, 61.7 mmol) and DME (15 mL) were added to a reactor previously inerted with nitrogen. TEPA (15.9 g, 70.9 mmol) was added at a rate such that the temperature was maintained at <30 °C (ca. 1 h). The reaction mixture was stirred until complete dissolution was observed (ca. 30 min). A solution of **3** in DME (5 g, 30.8 mmol and 10 g of DME) was added while maintaining the temperature between 20 and 30 °C. The reaction mixture was concentrated by distilling DME under vacuum at <60 °C until a concentration of ca. 1 M in **3** was achieved (distillate volume ca. 19 mL).[10] The reaction mixture was stirred at ca. 60 °C (12−15 h) until the HPLC area percent of **3** was <2 relative to the product **2a**. The temperature of the reaction mixture was increased to ca. 70 °C and maintained at this temperature (8−10 h) until the combined HPLC area percent of **3** and intermediate **7** was <2 relative to that of the product. The reaction mixture was cooled to <40 °C, and water (60 mL) was added. For the hydrolysis of **2a**, sodium hydroxide (50 wt %, 14.8 g, 185 mmol) was added, and the reaction mixture was heated to 50−60 °C for ca. 2 h. The reaction mixture was cooled to 0−10 °C, and 85% phosphoric acid (4 mL) was added to lower the pH from ca. 14 to ca. 7. EtOAc (90 mL) was added, and the pH of the biphasic mixture was further lowered to ca. 4 with 85% phosphoric acid (7 mL). The phases were separated, and the upper rich EtOAc phase containing **2b** (5.6 g, yield 88%, HPLC purity 99% (*R*,*R*)-isomer) was concentrated at 80 °C and atmospheric pressure until the moisture content of the solution was <0.1% (w/v). This solution was suitable for subsequent reactions leading to **1**.

An analytical sample of **2b** was prepared by evaporating the EtOAc solution to an oil and then crystallizing from MTBE−heptane: ^{1}H NMR ($CDCl_3$) δ 1.3 (m, 1H), 1.6 (m, 1H), 1.8 (m, 1H), 2.4 (m, 1H), 3.2 (m, 2H), 4.5 (m, 2H), 6.4 (d, **J** 1H), 6.6 (d, **J** 1H), 6.9 (t, **J** 1H), 9.6 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 16.54, 22.62, 24.8, 28.49, 71.05, 107.74, 116.31, 126.66, 128.29, 136.05, 159.79, 179.56 ppm. MS 203 $[M - H]^-$.

Characterization of intermediate **7** (M = H) by LC/MS: 387 $[M + H]^+$, 404 $[M + NH_4]^+$, 790 $[2M + NH_4]^+$.

(10) A peroxide inhibitor (BHT) was added to the DME distillate.

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