TIPSOTf-Promoted Tandem Reaction through Rearrangement of Epoxides into Aldehydes with Selective Alkyl Migration Followed by Prins-Type Cyclization to Cyclopentanes

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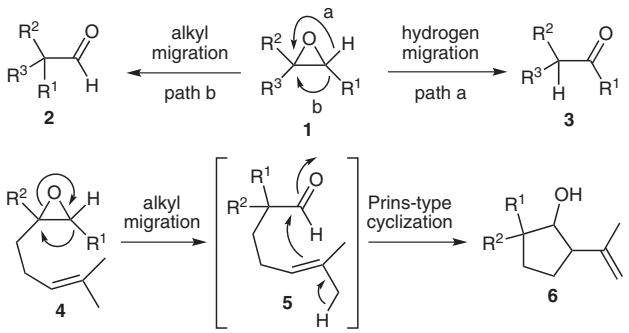
Abstract: The tandem reaction of trisubstituted epoxides to cyclopentanes promoted by TIPSOTf in nitromethane has been found. It consists of stereospecific rearrangement of epoxides into aldehydes accompanied with selective alkyl migration and subsequent Prins-type cyclization of the aldehydes generated to cyclopentanes.

Key words: cyclization, epoxides, rearrangement, steric hindrance, tandem reaction

Lewis acid promoted rearrangement of epoxides into carbonyl compounds is one of the most useful tools in organic synthesis.[1] The rearrangement has widely been applied to the synthesis of various biologically active natural and non-natural products;[2] however, it is well known that the yield and regio- and stereoselectivity of these rearrangements markedly depend on the mode of substituents on the ring and the reaction conditions.[3] The rearrangement of trisubstituted epoxide **1** takes place with hydrogen (path a) or alkyl (path b) migration to produce the corresponding ketone **3** or aldehyde **2**, respectively (Scheme 1). Although considerable efforts have been devoted to the development of efficient reagents and catalysts which allow access to ketone **3**,[4] only a few examples are documented on alkyl migration that allows access to aldehyde **2**.[5,6] On the other hand, tandem reactions are currently of great interest because they offer a convenient and economical way to prepare desired organic molecules.[7] Recently, we fortuitously encountered the tandem reaction that is thought to proceed via the TIPSOTf-promoted rearrangement of epoxide **4** into aldehyde **5** with selective alkyl migration followed by Prins-type cyclization to five-membered ring **6**. Such tandem reaction has never been reported to our knowledge. In this paper, we report the course of the findings and the results examined with some substrates.

Previously, we developed the regioselective 6-*endo* cyclization of bishomoepoxy alcohol **7a** (R^1 = H) to THP **8** promoted by TIPSOTf in the presence of 2,6-lutidine in nitromethane (entry 1 in Table 1).[8] This reaction is susceptible to solvents, and so treatment of **7a** (R^1 = H) with R^2OTf in dichloromethane afforded allylic silyl ethers **10a** as the major product (entries 2 and 3). We guessed that in nonpolar dichloromethane the cleavage of C6–O bond would be slower than that in polar nitromethane; therefore, during the cleavage of C6–O bond the hydroxy group suffered from silylation to produce epoxy silyl ether **11**. Since the oxygen of the silylated ether loses nucleophilicity, the epoxide would open into the allylic silyl ethers **10a** (like in E2 elimination). To demonstrate this we prepared the epoxy silyl ether **7b** (R^1 = TMS) which was subjected to the same condition as that of entry 2 in Table 1 to give **10a** (R^2 = TMS) in a similar ratio and yield according to our expectation (entry 4, Table 1).



Scheme 1 The mode of rearrangement of epoxide **1** and our tandem reaction of epoxide **4** to five-membered ring **6**

At that time we also tried treating the epoxy silyl ether **7b** (R^1 = TMS) under the condition of the 6-*endo* cyclization, and it was found that five-membered ring products **12a** and **12b** are unexpectedly formed in a ratio of 3.2:1 (entry 5).[9] The relative stereochemistry of the cyclopentanes **12a** and **12b** was unambiguously determined by diagnostic NOEs observed between the protons shown by arrows in the NOESY spectra.

The production of cyclopentanes **12a** and **12b** from epoxide **7b** (R^1 = TMS) might be rationalized as shown in Scheme 2. First, as soon as TIPSOTf coordinates to the epoxide oxygen, the C6–O bond begins cleaving in polar nitromethane and the epoxide rearrangement would occur. Then the alkyl group would migrate instead of hydrogen so as to avoid steric repulsion with the bulky Lewis acid.[5] Further, the generated aldehyde could undergo a nucleophilic attack under the condition by the intramolecular π-bond at an appropriate position to provide cyclized products. The major product **12a** might be produced by way of the most stable transition state **B** without such ster-

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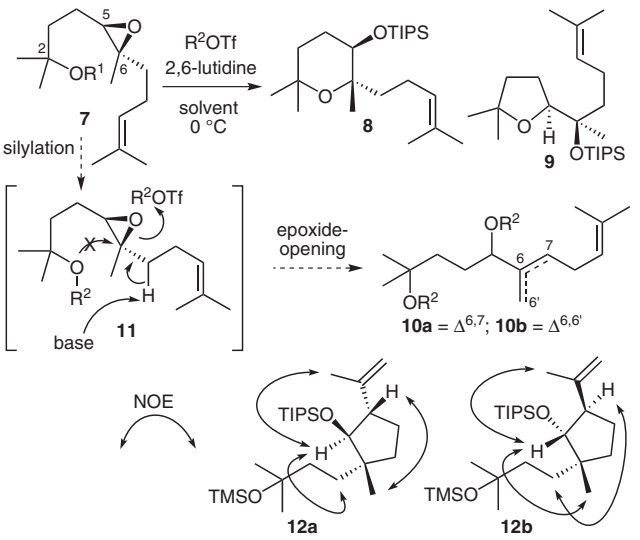
Table 1 Reactions of Epoxides **7** Promoted by R^2OTf in the Presence of 2,6-Lutidine under Various Conditions

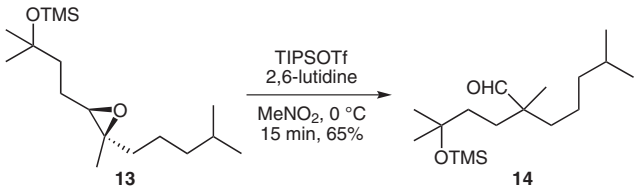


Entry	**7** (R^1)	R^2OTf	Solvent	Product (ratio),[a] yield[b]
1[c]	**7a** (H)	R^2 = TIPS	$MeNO_2$	**8/9** (15:1), 83%
2[c]	**7a** (H)	R^2 = TMS	CH_2Cl_2	**10a/10b** (9:1), 70%
3[c]	**7a** (H)	R^2 = TIPS	CH_2Cl_2	**10a**, 38%; **8/9** (2.7:1), 34%
4	**7b** (TMS)[d]	R^2 = TMS	CH_2Cl_2	**10a/10b** (10:1), 65%
5	**7b** (TMS)[d]	R^2 = TIPS	$MeNO_2$	**12a/12b** (3.2:1), 64%

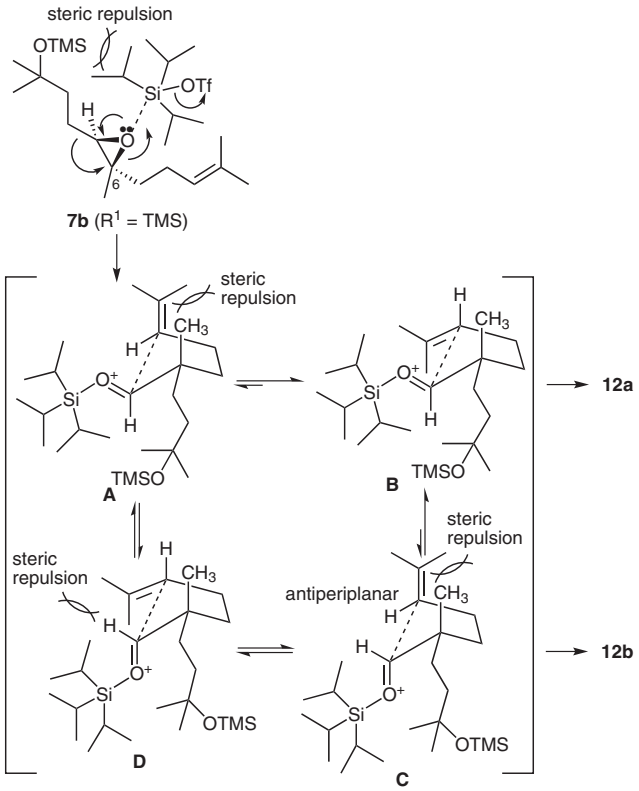
[a] The ratio was determined by integration of the ^1H NMR spectra of the mixture.
[b] Isolated yield.
[c] These data are cited from ref. 8.
[d] Epoxide **7b** (R^1 = TMS) was prepared by silylation of **7a** (R^1 = H) (TMSCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 16 h, 83%).

ic repulsion as exists in other transition states **A**, **C**, and **D**. The minor product **12b** might be formed through only one acyclic extended transition state **C** having antiperiplanar π-bonds.[10]

To evidence the intermediacy of aldehyde in the tandem reaction, we tried to trap the rearrangement product aldehyde such as **5**. When saturated epoxide **13**, which was prepared by hydrogenation of **7b** (R^1 = TMS; H_2, Pd/C, THF, r.t., 2.5 h, 76%), was treated under the condition of the tandem reaction, alkyl-migrated aldehyde **14** could be isolated (Equation 1).

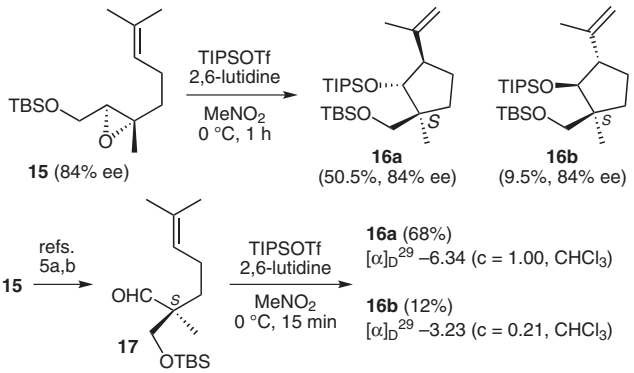


Equation 1



Scheme 2 Possible transition states **B** and **C** leading to **12a** and **12b**, respectively

Next, we examined the chirality transfer ability of the epoxide rearrangement using an optically active substrate. The known optically active epoxide **15** (84% ee)[5] was subjected to the tandem reaction to afford diastereomeric cyclopentanes **16a** {$[\alpha]_D^{21}$ –6.35 (c = 0.97, $CHCl_3$)}, and **16b** {$[\alpha]_D^{29}$ –4.09 (c = 0.33, $CHCl_3$)}[11] with virtually the same optical purity[12] as that of the starting material in a ratio of 5.3:1 (Scheme 3). The relative configuration of **16a** and **16b** was elucidated on the basis of such NOE experiments as shown in **12**. The absolute configuration of **16a** and **16b** was determined by comparing their optical rotations with those of cyclopentanes **16a** and **16b** obtained in a similar ratio of 5.6:1 from the known *S*-aldehyde **17** reported by Yamamoto and co-workers.[5a,b] Thus, it has been found that in the tandem reaction the first epoxide rear-



Scheme 3 The tandem reaction of optically active epoxide **15** to five-membered rings **16a** and **16b** with integrity of the optical purity

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rangement takes place accompanying inversion of configuration at the quaternary carbon of the epoxide without any loss of optical purity, and the second cyclization should indeed proceed from an aldehyde intermediate to form cyclopentanes.

The TIPSOTf-promoted tandem reaction was further examined for some epoxides (Table 2). Epoxides **18** and **19**,[5b,c,12] diastereomeric to **7b** (R^1 = TMS) and **15**, similarly underwent the tandem reaction providing **12a**, **12b** and *ent*-**16a**, *ent*-**16b** in moderate yields, respectively (entries 1 and 2). This indicates that in the first epoxide rearrangement alkyl groups selectively migrate irrespective of the relative stereochemistry of the epoxide.[5]

Table 2 The TIPSOTf-Promoted Tandem Reaction of Some Epoxides[a]

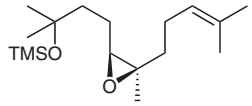
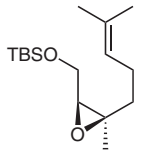
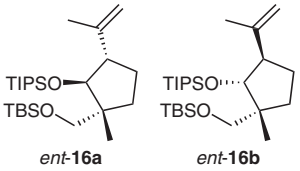
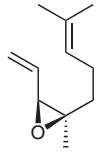
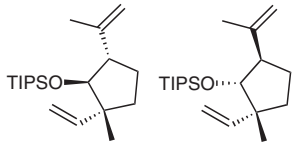
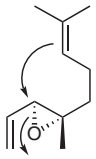
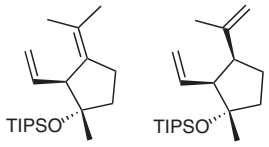
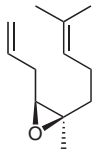
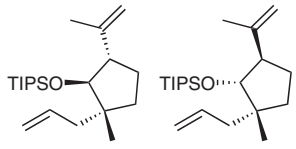
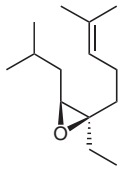
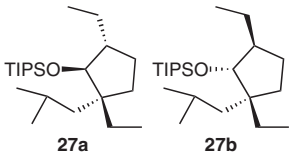
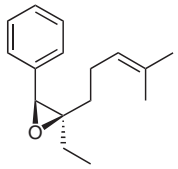
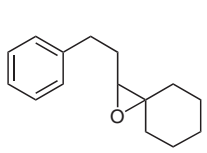
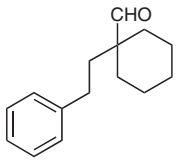
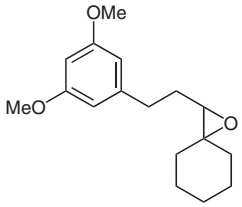
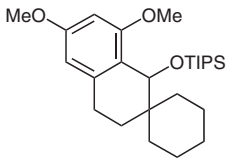
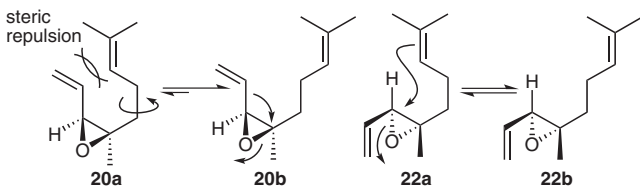
Entry	Epoxide	Time, Product[b] (ratio),[c] yield[d]
1	 **18**	1 h, **12a/12b** (3.6:1), 54%
2	 **19** (74% ee)	 *ent*-**16a** *ent*-**16b** 15 min, *ent*-**16a** (74% ee), 41.7%; *ent*-**16b**, 8.3%
3	 **20**	 **21a** **21b** 30 min, **21a/21b** (2.8:1), 80%
4	 **22**	 **23a** **23b** 1 h, **23a/23b** (1.3:1), 78%
5	 **24**	 **25a** **25b** 1 h, **25a/25b** (1.5:1), 55%
6	 **26**	 **27a** **27b** 15 h, **27a/27b** (1.3:1), 53%; recovered **26**, 22%

Table 2 The TIPSOTf-Promoted Tandem Reaction of Some Epoxides[a] (continued)

Entry	Epoxide	Time, Product[b] (ratio),[c] yield[d]
7	 **28**	0 °C, 1 h, then reflux, 20 h, recovered **28**, 82%
8	 **29**	 **30** 30 min, 78%
9	 **31**	 **32** 15 min, 36%

[a] The reaction was performed at 0 °C for the indicated time under a nitrogen atmosphere by treating the starting epoxide in the presence of 2,6-lutidine in $MeNO_2$ with TIPSOTf, unless otherwise noted.
[b] The stereochemistry of the product was determined by NOE experiments.
[c] The ratio was determined by integration of the ^1H NMR spectra of the mixture except for entry 2.
[d] Isolated yield.

Vinyl-substituted epoxide **20** afforded products **21a** and **21b** in a relatively good yield, probably due to higher migrating ability of a vinyl group compared to other alkyl groups (entry 3).[4j,13] To our surprise, epoxide **22**, diastereomeric to **20**, did not give predictable cyclopentanes such as **21** but a different type of cyclopentanes **23a** and **23b** that were directly cyclized at the allylic carbon of the epoxide (entry 4). In the case of epoxide **22** with hydrogen *syn* to the attacking π-bond, the direct cyclization might occur because the π-bond can more easily approach the reactive allylic carbon than in the case of epoxide **20** with the *syn* vinyl group as shown in Scheme 4.



Scheme 4 Conformation of vinyl epoxides **20** and **22**

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Although tandem reaction products **25a**, **25b** and **27a**, **27b** were also obtained from epoxides **24** and **26**, respectively, in the reaction of **26** the starting material was recovered in 22% yield after 15 hours (entries 5 and 6). Furthermore, epoxide **28** was recovered in 82% yield, even after the reaction was carried out at 0 °C for one hour and then under reflux for 20 hours (entry 7). These results indicate that the first epoxide rearrangement promoted by bulky TIPSOTf is subtly influenced by steric circumstances around the epoxide function. Next, aromatic rings were investigated in place of double bonds as the intramolecular nucleophile. Although epoxide **29** was only rearranged into aldehyde **30** (entry 8), epoxide **31** bearing a more nucleophilic dimethoxyphenyl group provided a tandem reaction product **32**, demonstrating that the second cyclization can form not only five-membered rings but also a six-membered ring (entry 9).

In conclusion, we have demonstrated that the TIPSOTf-promoted tandem reaction via stereospecific rearrangement of trisubstituted epoxides into aldehydes followed by the electrophilic cyclization of the aldehydes generated five- and six-membered ring compounds. Further scope and limitations of the tandem reaction and its application to biologically important natural products are under investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **Typical Procedure for the Tandem Reaction**: To a solution of epoxide **7b** (R^1 = TMS, 30.0 mg, 0.100 mmol), prepared from **7a** (R^1 = H, ref. 8) according to footnote d in Table 1, in nitromethane (1.0 mL) were successively added dropwise 2,6-lutidine (92 μL, 0.703 mmol) and triisopropylsilyl triflate (0.135 mL, 0.502 mmol) under a nitrogen atmosphere at 0 °C, and the mixture was stirred at the same temperature for 45 min. H_2O was added to the solution, and the aqueous layer was extracted with hexane. The organic layer was washed with brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–benzene, 98:2) on silica gel to afford a mixture of cyclopentanes **12a** and **12b** (29.4 mg, 64% yield) in a ratio of 3.2:1 as a colorless oil; R_f 0.58 (hexane–benzene, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.77 (s, 1 H), 4.71 (s, 1 H), 3.88 (d, *J* = 6.6 Hz, 0.24 H), 3.82 (d, *J* = 7.3 Hz, 0.76 H), 2.53–2.64 (m, 1 H), 1.14–1.93 (m, 8 H), 1.72 (s, 3 H), 1.22 (s, 1.44 H), 1.20 (s, 4.56 H), 0.97–1.12 (m, 21 H), 0.94 (s, 0.72 H), 0.90 (s, 2.28 H), 0.10 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.3, 147.2, 111.1, 110.7, 84.1, 77.2, 74.0, 54.8, 53.7, 45.6, 45.4, 39.9, 39.4, 35.3, 34.8, 34.2, 29.8, 26.7, 24.1, 20.0, 19.7, 18.6, 18.5, 18.4, 13.4, 13.3, 2.7, 2.6. IR (neat): 3076, 1641, 1462, 1378, 1107, 882 cm^{-1}. HRMS (FAB): *m/z* [M – H$^+$] calcd for $C_{26}H_{53}O_2Si_2$: 453.3584; found: 453.3591.

(10) (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

(11) **Compound 16a**: R_f = 0.62 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.77–4.81 (m, 1 H), 4.68–4.72 (m, 1 H), 4.24 (d, *J* = 7.3 Hz, 1 H), 3.44 (d, *J* = 9.5 Hz, 1 H), 3.30 (d, *J* = 9.8 Hz, 1 H), 2.59 (dt, *J* = 9.9, 7.1 Hz, 1 H), 1.82–1.93 (m, 1 H), 1.74 (dt, *J* = 12.2, 8.4 Hz, 1 H), 1.72 (s, 3 H), 1.32–1.42 (m, 1 H), 1.27 (ddd, *J* = 12.4, 7.9, 4.6 Hz, 1 H), 1.00–1.09 (m, 21 H), 0.90 (s, 9 H), 0.88 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.3, 111.0, 77.3, 67.6, 54.2, 48.0, 32.6, 26.8, 25.9, 19.6, 18.4, 18.3, 17.9, 13.3, –5.5, –5.6. IR (neat): 3079, 1644, 1463, 1254, 1087, 835 cm^{-1}. HRMS (FAB): *m/z* [M$^+$] calcd for $C_{25}H_{52}O_2Si_2$: 440.3506; found: 440.3515.

Compound 16b: R_f 0.51 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74–4.78 (m, 1 H), 4.70–4.74 (m, 1 H), 3.97 (d, *J* = 7.1 Hz, 1 H), 3.63 (d, *J* = 10.0 Hz, 1 H), 3.50 (d, *J* = 10.0 Hz, 1 H), 2.63 (dt, *J* = 9.3, 7.0 Hz, 1 H), 1.81–1.94 (m, 2 H), 1.72 (s, 3 H), 1.32–1.44 (m, 1 H), 1.18–1.31 (m, 1 H), 0.97–1.10 (m, 21 H), 1.02 (s, 3 H), 0.90 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.2, 110.9, 83.9, 66.5, 55.3, 48.0, 33.1, 27.3, 26.0, 22.9, 19.9, 18.39, 18.37, 18.32, 13.2, –5.45, –5.49. IR (neat): 3079, 1642, 1463, 1086,

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835 cm^{-1}. HRMS (FAB): *m/z* [M – H^+] calcd for $C_{25}H_{51}O_2Si_2$: 439.3427; found: 439.3422.

(12) (a) The optical purities of **15** and **19** were determined to be 84% ee and 74% ee by derivatization of epoxy alcohols, which were prepared from geraniol and nerol by Sharpless asymmetric epoxidation using diethyl L-(+)-tartrate (ref. 5), to their (*R*)-α-methoxy-α-trifluoromethylphenylacetyl (MTPA) esters and integration of the ^1H NMR and ^{19}F NMR spectra, respectively: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) The optical purities of **16a**, **16b**, and *ent*-**16a** were determined to be 84% ee, 84% ee, and 74%ee, respectively, by derivatization of desilylated diols in **16a**, **16b**, and *ent*-**16a** to their di(*R*)-MTPA esters and integration of the ^1H NMR (**16a** and **16b**) and ^{19}F NMR (*ent*-**16a**) spectra.

(13) Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605.

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