A NEW STEREOSELECTIVE SYNTHESIS OF (-)-PERIPLANONE-B[#]

Shigefumi Kuwahara and Kenji Mori*
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1,
Bunkyo-ku, Tokyo 113, Japan

Abstract - Optically pure (-)-periplanone-B, a sex pheromone component of the American cockroach (*Periplaneta americana*), was synthesized from (*S*)-3-cyclohexene-1-carboxylic acid in 18 steps. About 300 mg of the crystalline pheromone was obtained in 11% overall yield.

Periplanone-B **1**,[1] the female-produced sex pheromone of the American cockroach, has been synthesized as the racemate by four research groups[2] since Still's first synthesis[2a] based on ingenious stereocontrol in medium-ring systems. The chiral synthesis of (-)-**1** has also been achieved.[3] However, the previous synthesis required as many as 28 steps from (+)-dihydrolimonene, resulting in only 0.5% overall yield.[3] This result prompted us to plan an alternative and more efficient synthesis of (-)-**1**.

Our synthetic plan is shown in Fig. 1. We adopted a ten-membered ring enone **2** as our synthetic intermediate so as to make our synthesis stereoselective with respect to C-2,3-epoxidation. This enone **2**(R=TBDPS) was shown, in Takahashi's synthesis of (±)-**1**, to give the desired 2,3-β-epoxide exclusively when treated with *t*-BuOOK.[2d] In order to obtain **2** by his intramolecular alkylation route, more than 15 steps were required.[2d] We therefore chose the anionic oxy-Cope rearrangement[4] of **3** for the simpler construction of **2**.[2a,2b,2c] Preparation of **3** from **5** was successfully achieved in three steps by using organoselenium chemistry[5] as described later.

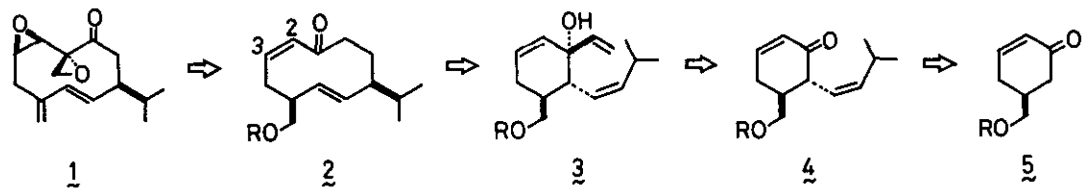
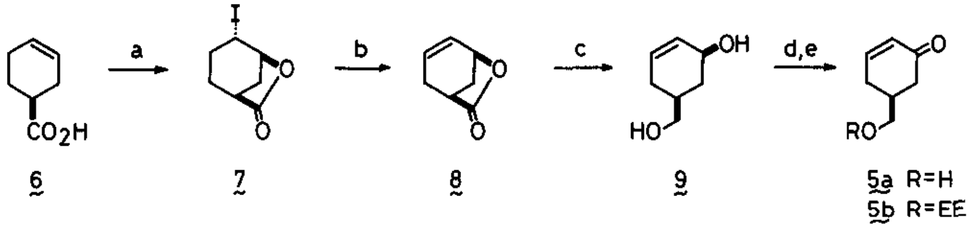


Fig. 1. Retrosynthetic analysis of (-)-periplanone-B

[#] Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.

For the preparation of the monosubstituted cyclohexenone 5 with (S)-configuration, our synthesis began with the iodolactonization of **6**,[6] $[\alpha]_D^{23}$ -99° ($CHCl_3$), to give **7** (Fig. 2). ^1H Nmr(400MHz) analysis of the resulting iodolactone **7** in the presence of Pirkle's chiral solvating agent[7] showed the iodolactone to be optically pure. Treatment of **7** with DBU followed by LAH reduction gave a diol **9** via **8**. Selective oxidation of **9** with MnO_2 gave **5a**, of which OH group was then protected as an ethoxyethyl ether **5b**. Each of these reactions proceeded almost quantitatively, so **5b** was obtained in 86% overall yield from **6**.

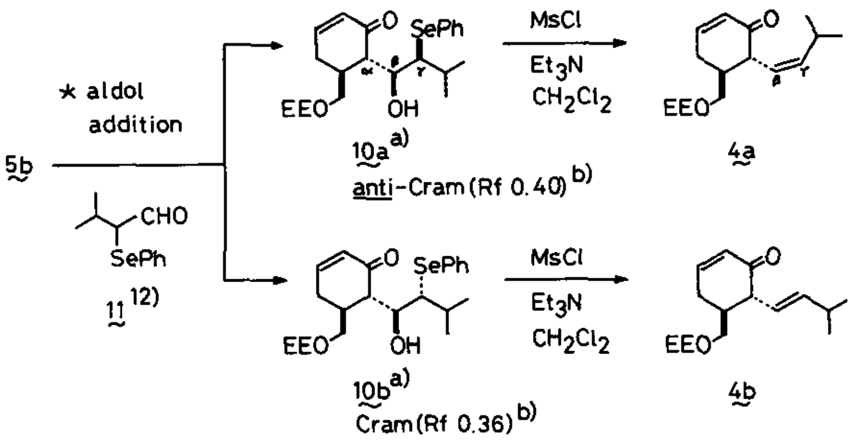


a) KI_3, $NaHCO_3$aq., CH_2Cl_2: b) DBU, benzene; c) LAH, THF; d) MnO_2, $CHCl_3$; e) ethyl vinyl ether, PPTS, CH_2Cl_2.

Fig. 2. Preparation of 5

The conversion of **5b** into **4**(R=EE) was pivotal in our synthesis, because (Z)-geometry of the double bond on the side chain of **3** was essential for the construction of **2** via oxy-Cope pathway.[4,2a,2c] We tried a two-step procedure without protection of the enone system. This method was originally developed by Kowalski[8] and Clive[9] independently (Fig. 3). As expected from the usual preference for the Cram-selective addition of organometallics to α-selenoaldehydes[10] and the subsequent stereospecific anti-elimination of β-hydroxyselenide[11], condition A gave the trans-isomer **4b**($J_{\beta,\gamma}$=16 Hz) via **10b** predominantly. Surprisingly, the ratio of **4a**($J_{\beta,\gamma}$=10 Hz) to **4b** reversed by changing the reaction condition from A into B. Furthermore, when the temperature of the reaction mixture in THF was raised rapidly from -78°C to -15°C during about 3 min (condition C), the aldol(s) **10b** leading to **4b** decomposed. Consequently, **4a** was obtained in 93% selectivity. By the combination of condition C and careful chromatographic purification of **10a**, pure **4a** could be obtained in 51% isolated yield from **5b**. At present, these results seem to be ascribable merely to the solvent and thermal instability of **10b**, judging from some additional experiments. Detailed discussion will be described in a full paper.

The disubstituted cyclohexenone **4a** thus obtained was subjected to the reaction with vinyllithium in ether[2a] to give **3**, which produced **2** on treatment with KH in DME[13] in 64% yield (Fig. 4). The ten-membered ring enone **2** was converted to **12b** (mp 124.5-125°C) via **12a**



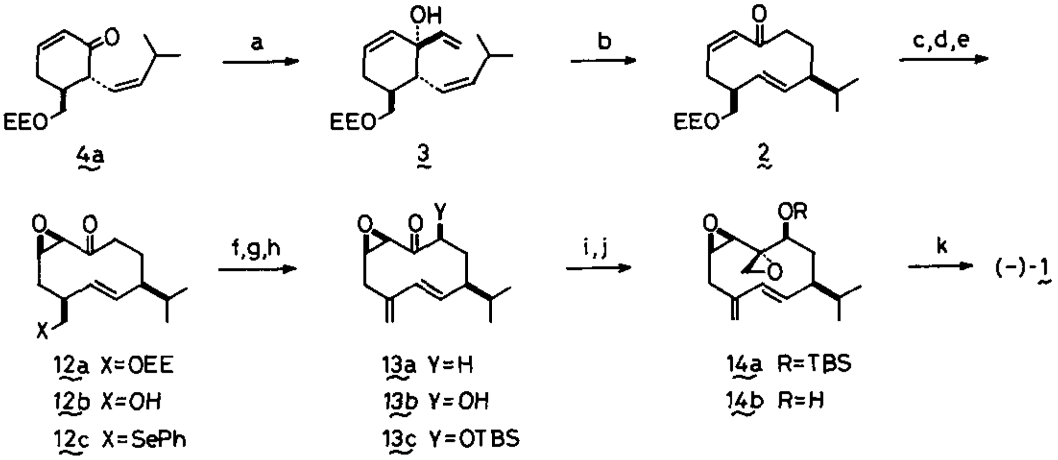
*condition	yield(%)c)	
	4a	**4b**
A i) LDA, TMSCl; ii) MeLi, $ZnCl_2$, **11**, ether, -78°C	11	64
B LDA, **11**, THF, -78°C, 20 min	55(60)	30(40)
C LDA, **11**, THF, -78°C, 20 min then -15°C, 3 min	51(93)	<5(7)

a) The relative stereochemistry between C-α and C-β was not determined.

b) Merck Kieselgel 60, Art. 5715; n-hexane/ether(2:5).

c) Glc ratios are shown in parentheses.

Fig. 3. Two-step conversion of **5b** into **4a**



a) vinyllithium, ether (86%); b) KH, 18-crown-6, DME (74%); c) KH, t-BuOOH, THF; d) PPTS, EtOH (74%); e) (o-NO_2)PhSeCN, n-Bu_3P, THF (99%); f) H_2O_2, THF (90%); g) $LiN(TMS)_2$, MoO_5·HMPA·Py, THF, (86%); h) TBSCl, imidazole, DMF; i) Me_3SI, n-BuLi, THF; j) n-Bu_4NF, THF (73%); k) PDC, DMF (92%).

Fig. 4. Synthesis of (-)-periplanone-B

by epoxidation and deprotection. ^{1}H Nmr(400MHz) analysis supported that **12b** was diastereomerically pure in accord with Takahashi's result.[2d] Selenylation of **12b** to **12c** followed by oxidative elimination of PhSeOH gave **13a**, mp 49.5-50.5°C. α-Hydroxylation[3,14] of the ketone **13a** yielded **13b**, mp 116-119°C. According to the previous synthesis[3], **13b** was treated successively with TBSCl, dimethylsulfonium methylide and Bu_4NF to give periplanol-B **14b** [mp 115-116.5°C; $[\alpha]_D^{21}$ -468° (ether)][15] via **13c** and **14a**. Finally oxidation of **14b** gave (-)-periplanone-B (-)-**1**, mp 55.5-57.5°; $[\alpha]_D^{21}$ -552° (n-hexane)(lit.[3b] mp 57.0-57.5°; $[\alpha]_D^{26}$ -553°). Its ir and ^{1}H nmr spectra were identical with those of an authentic sample.[3b] The present 18-step synthesis of (-)-periplanone-B was accomplished in 11% overall yield to give about 300 mg of (-)-**1**. This is the highest yield that ever has been reported.

REFERENCES AND NOTES

1. C. J. Persoons, P. E. J. Verwiel, E. Talman, and F. J. Ritter, J. Chem. Ecol., 1979, **5**, 219 and references cited therein.
2. a) W. C. Still, J. Am. Chem. Soc., 1979, **101**, 2493. b) S. L. Schreiber and C. Santini, ibid., 1984, **106**, 4038. c) H. Hauptmann, G. Mühlbauer, and N. P. C. Walker, Tetrahedron Lett., 1986, **27**, 1315. d) T. Takahashi, Y. Kanda, H. Nemoto, K. Kitamura, J. Tsuji, and Y. Fukazawa, J. Org. Chem., 1986, **51**, 3393.
3. a) T. Kitahara, M. Mori, K. Koseki, and K. Mori, Tetrahedron Lett., 1986, **27**, 1343. b) T. Kitahara, M. Mori, and K. Mori, Tetrahedron, 1987, **43**, 2689.
4. D. A. Evans and A. M. Golob, J. Am. Chem. Soc., 1975, **97**, 4765.
5. C. Paulmier, 'Selenium Reagents and Intermediates in Organic Synthesis,' Pergamon Press, Oxford, 1986.
6. a) H. M. Schwartz, W-S Wu, P. W. Marr, and J. B. Jones, J. Am. Chem. Soc., 1978, **100**, 5199. b) T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, Tetrahedron Lett., 1985, **26**, 3095.
7. W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, J. Org. Chem., 1977, **42**, 384.
8. C. J. Kowalski and J-S Dung, J. Am. Chem. Soc., 1980, **102**, 7950.
9. D. L. J. Clive, C. G. Russell, and S. C. Suri, J. Org. Chem., 1982, **47**, 1632.
10. a) A. M. Léonard-Coppens and A. Krief, Tetrahedron Lett., 1976, 3227. b) S. Halazy and A. Krief, ibid., 1981, **22**, 1833. c) T. K. Sarkar and S. K. Ghosh, ibid., 1987, **28**, 2061.
11. H. J. Reich, F. Chow, and S. K. Shah, J. Am. Chem. Soc., 1979, **101**, 6638.
12. This was prepared from isovaleraldehyde by treatment with morpholinobenzeneselenenamide in 64% yield, bp 109-116°C(0.5 Torr). P. Lerouge and C. Paulmier, Tetrahedron Lett., 1984, **25**, 1983.
13. D. A. Evans, D. J. Baillargeon, and J. V. Nelson, J. Am. Chem. Soc., 1978, **100**, 2242.
14. E. Vedejs, D. A. Engler, and J. E. Telschow, J. Org. Chem., 1978, **43**, 188.
15. The 100% enantiomeric purity of **14b** was confirmed by the MTPA method.[3b]

Received, 30th August, 1988