# ASYMMETRIC INDUCTION IN INTRAMOLECULAR [5 + 2] CYCLOADDITION OF 2-(4-ALKENYL)-5-BENZOYLOXY(OR 5-SILYLOXY)-4-PYRONES INVOLVING MIGRATION OF THE PYRONE O-5 GROUP TO O-4

Naoki Ohmori, Miki Yoshimura, and Katsuo Ohkata*

Department of Chemistry, Faculty of Science, Hiroshima University,
1-3-1 Kagamiyama, Higashi-Hiroshima 739, Japan

**Abstract** - Heating of the title compounds (**1a,b**) at 130 °C in *o*-dichlorobenzene afforded [5+2] annulation products (**2a,b**) in 70% yield; 27-33% d.e. via 3-oxidopyrylium ylide. Reaction of the title compounds (**1b,c**) in the presence of $ZnCl_2$ at 40 °C furnished [5+2] annulation products (**2b,c**) in 23-64% yield and 53-59% d.e. In the event, treatment of the 5-silyloxy derivatives (**1d,e**) with TBSOTf in the presence of 2,6-lutidine at even 20 °C for 16 h gave [5+2] annulation products (**2d,e**) with 75% d.e. and 78% d.e. in high yields, respectively.

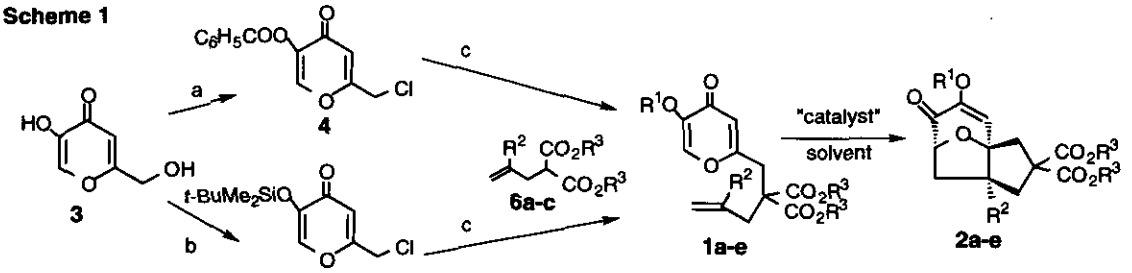
Efficient, expeditious approaches to stereodefined bicyclo[5. 3. 0]decane framework have been sought due to increasing awareness of the occurrence of these substructures in a wide variety of bioactive natural products, including sesquiterpenes, diterpenes, and troponoids.[1,2] Convenient methodology for the synthesis of a seven-membered ring involves trapping oxidopyrylium species with various olefins. Notwithstanding, less attention has been paid to the asymmetric induction in the [5 + 2] cycloadditions compared with the [4 + 2] cycloadditions.

Wender *et al.* found that the thermal [5 + 2] cycloaddition at high temperature (200 °C) proceeded to construct bicyclo[5. 4. 0]undecane framework with high diastereoselectivity in the course of the synthesis of phorbol.[3a] Magnus *et al.* have also developed the diastereoselective cycloaddition (60-80% d.e.) of the pyrylium ylide-alkene during the synthetic investigations of taxane diterpenes.[3b] These high diastereoselective reactions would be attributable to the stereogenic center at the α-position (at the most neighbor position) in the side chain of 3-oxidopyrylium ylide. Recently, the asymmetric synthesis of the oxabicyclo[3. 2. 1]octa-2,6-diene derivatives was found by using (*S*)-lactate or (*R*)-pantolactone as chiral auxiliaries on the carbenoid.[4] We report here the asymmetric induction in the intramolecular [5 + 2] cycloaddition of 2-(4-alkenyl)-5-benzoyloxy(or 5-silyloxy)-4-pyrones (**1a-e**) to give the adducts (**2a-e**) by means of chiral auxiliaries (-)-menthyl and (-)-8-phenylmenthyl as shown in Scheme 1.

Reaction of commercially available kojic acid (**3**) with benzoyl chloride, followed by chlorination with thionyl chloride afforded 5-benzoyloxy-2-chloromethyl-4-pyrone (**4**) in 41% yield over the two steps.[5] Treatment of **4** with di-(-)-menthyl 2-propenylmalonate (**6a**), di-(-)-menthyl 2-methyl-2-

propenylmalonate (**6b**) and di-(-)-8-phenylmenthyl isobutenylmalonate (**6c**) gave 2-(4-alkenyl)-5-benzoyloxy-4-pyrones (**1a-c**) in 39%, 28%, and 13% yields, respectively.[6] Reaction of kojic acid (**3**) with thionyl chloride followed by O-5 silylation afforded chloride (**5**) (76% yield over the two steps).[7] Reaction of **5** with **6b,c** gave 2-(4-alkenyl)-5-silyloxy-4-pyrone (**1d**) and (**1e**) in 60% and 34% yields, respectively. In the preparation of **1a-c** and **1e**, a large amount of starting materials was recovered. These yields were calculated to be 40-97% on the basis of the recovery.

**Scheme 1**




*Reagents and Solvents:*
a: (1) $C_6H_5COCl$, KOH in EtOH-$H_2O$; (2) $SOCl_2$, pyridine in THF
b: (1) $SOCl_2$, pyridine in THF; (2) *t*-$BuMe_2SiCl$, $Et_3N$, DMAP in THF
c: NaH, NaI in THF and then **6a-c**

**6a**: $R^2$ = H, $R^3$ = (-)-menthyl
**6b**: $R^2$ = Me, $R^3$ = (-)-menthyl
**6c**: $R^2$ = Me, $R^3$ = (-)-8-phenylmenthyl

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1a, 2a** | $C_6H_5CO$ | H | (-)-menthyl |
| **1b, 2b** | $C_6H_5CO$ | Me | (-)-menthyl |
| **1c, 2c** | $C_6H_5CO$ | Me | (-)-8-phenylmenthyl |
| **1d, 2d** | *t*-$BuMe_2Si$ | Me | (-)-menthyl |
| **1e, 2e** | *t*-$BuMe_2Si$ | Me | (-)-8-phenylmenthyl |

Heating of **1a,b** in *o*-dichlorobenzene at 130 °C for 2 d gave the adducts (**2a**) (71% yield; 33% d.e.) and (**2b**) (73% yield; 27% d.e.), respectively (entries 1, 2). Two diastereomers of **2b** were separated by preparative TLC on silica gel.[8] Reaction of **1b** in the presence of $ZnBr_2$ in the same solvent at 80 °C gave **2b** (50% yield; 34% d.e.) (entry 4). When $ZnCl_2$ in *o*-dichlorobenzene was used as the acid catalyst, the reaction of **1b** occurred at lower temperature (40 °C) for 4 d to give **2b** in higher stereoselectivity (23% yield; 56% d.e.) (entry 5). Treatment of **1c** with $ZnCl_2$ at 40 °C for 5 d in toluene afforded **2c** (64% yield; 59% d.e.) (entry 7).[9a] These results are summarized in Table 1. The Lewis acid promoted cycloaddition resulted in higher selectivity relative to that under heating (no catalyst) (entries 1, 2). The diastereoselectivity in the cycloaddition in which (-)-8-phenylmenthyl group was used as the chiral auxiliary (entry 7) was slightly increased compared with that utilized the (-)-menthyl group. The other catalysts ($TiCl_4$, $AlCl_3$) were all ineffective in the cycloaddition.

While migration of silyl group in 5-silyloxy-4-pyrone derivative occurred only at high temperature (200 °C),[3a] the migration is expected to proceed smoothly by means of silyl triflate. In the event, reaction of **1d** with *t*-butyldimethylsilyl triflate (3 eq) in the presence of 2,6-lutidine at even 20 °C for 16 h afforded the silyloxy derivative (**2d**) with 70% d.e. in quantitative yield (entry 8).[10] The smooth migration of the silyl group can be rationalized in terms of generation of the 3-oxidopyrylium ion species.[3a] The diastereoselectivity in the conversion of **1e** into **2e** was improved to 78% d.e. by utilizing the (-)-8-phenylmenthyl chiral auxiliary (entry 9).[9b] The stereochemistry of **2a-e** was determined to be an *exo*-isomer by considerations of the $^1H$ NMR spectral data: coupling constants and DIF-NOE measurements. Furthermore, angle strain at the fusion points of the oxatricyclo system also suggests *exo*-attack in the cycloaddition.[11]

**Table 1** Asymmetric [5+2] cycloaddition in **1a-e**

| entry | reactant | solvent[a] | conditions | product | yield (%) | d.e. (%)[b] | chiral auxiliary |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | A | 130 °C, 2 d | **2a** | 71 | 33 | (-)-menthyl |
| 2 | **1b** | A | 130 °C, 2 d | **2b** | 73 | 27 | (-)-menthyl |
| 3 | **1a** | A | $ZnBr_2$ (1eq), 80 °C, 15 h | **2a** | 76 | 34 | (-)-menthyl |
| 4 | **1b** | A | $ZnBr_2$ (1eq), 80 °C, 15 h | **2b** | 50 | 34 | (-)-menthyl |
| 5 | **1b** | A | $ZnCl_2$ (1eq), 40 °C, 4 d | **2b** | 23 | 56 | (-)-menthyl |
| 6 | **1b** | B | $ZnCl_2$ (2eq), 40 °C, 7 d | **2b** | 49 | 53 | (-)-menthyl |
| 7 | **1c** | B | $ZnCl_2$ (1eq), 40 °C, 5 d | **2c** | 64 | 59 | (-)-8-phenylmenthyl |
| 8 | **1d** | C[c] | TBSOTf (2eq), 20 °C, 16 h | **2d** | 96 | 70 | (-)-menthyl |
| 9 | **1e** | C[c] | TBSOTf (2eq), 20 °C , 16 h | **2e** | 78 | 78 | (-)-8-phenylmenthyl |

[a] solvent, A: *o*-dichlorobenzene, B: toluene, C: dichloromethane. [b] The diastereomeric excess was determined by $^1H$ NMR or HPLC. [c] in the presence of 2,6-lutidine (3 eq).

## ACKNOWLEDGMENTS

The measurements of NMR and HRMS were made using JEOL GSX-270 and JEOL SX-102A, respectively, at the Instrument Center for Chemical Analysis, Hiroshima University.

## REFERENCES AND NOTES

1. P. G. Sammes and L. J. Street, *J. Chem. Soc., Chem. Commun.*, 1983, 666; P. G. Sammes, *Gazz. Chim. Ital.*, 1986, **116**, 109; K. Ohkata and K. Akiba, *Adv. Heterocycl. Chem.*, ed. by A. R. Katritzky, Academic Press, New York, 1996, Vol. **65**, 283-374.
2. P. A. Wender, H. Y. Lee, R. S. Wilhelm, and P. D. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 8954; P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger, Jr., R. S. Wilhelm, and P. D. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 8957.
3. (a) P. A. Wender and F. E. McDonald, *J. Am. Chem. Soc.*, 1990, **112**, 4956; P. A. Wender and Mascareñas, *J. Org. Chem.*, 1991, **56**, 6267; P. A. Wender and J. L. Mascareñas, *Tetrahedron Lett.*, 1992, **33**, 2115. (b) W. E. Bauta, J. Booth, M. E. Bos, M. DeLuca, L. Diorazio, T. J. Donohoe, C. Frost, N. Magnus, P. Magnus, J. Mendoza, P. Pye, J. G. Tarrant, S. Thom and F. Ujjainwalla, *Tetrahedron,* 1996, **52**, 14081.
4. H. M. L. Davies, G. Ahmed, and M. R. Churchill, *J. Am. Chem. Soc.*, 1996, **118**, 10774.
5. M. E. Garst, B. J. McBride, and J. C. Douglass, III, *Tetrahedron Lett.*, 1983, **24**, 1675. Garst *et al.* have investigated such an intramolecular [5 + 2] cycloaddition of various substrates in racemic series.
6. All new compounds have been fully characterized by $^1H$ NMR and possess satisfactory exact mass.
7. A. Rumbo, L. Castedo, A. Mouriño, and J. L. Mascareñas, *J. Org. Chem.*, 1993, **58**, 5585; *J. Org. Chem.*, 1996, **61**, 6114.
8. *Selected spectroscopic data*: for the major isomer of **2b**: $^1H$ NMR (270 MHz, $CDCl_3$) δ: 8.10 (td, $J$ = 7.3, 1.5 Hz, 2H), 7.62 (tt, $J$ = 7.3, 1.5 Hz, 1H), 7.48 (t, $J$ = 7.8 Hz, 2H), 6.94 (s, 1H),

4.63 (dd, $J$ = 8.8, 1.5 Hz, 1H), 3.04 (d, $J$ = 14.2 Hz, 1H), 2.92 (d, $J$ = 14.7 Hz, 1H), 2.84 (d, $J$ = 14.7 Hz, 1H), 2.70 (dd, $J$ = 13.7, 8.8 Hz, 1H), 2.06 (d, $J$ = 14.2 Hz, 1H), 1.80 (dd, $J$ = 13.7, 1.5 Hz, 1H), 1.24 (s, 3H), and the other signals assigned to the menthyl moiety; for the minor isomer of **2b:** δ: 8.10 (td, $J$ = 7.3, 1.5 Hz, 2H), 7.62 (tt, $J$ = 7.3, 1.5 Hz, 1H), 7.48 (t, $J$ = 7.8 Hz, 2H), 6.89 (s, 1H), 4.63 (dd, $J$ = 8.8, 1.5 Hz, 1H), 3.21 (d, $J$ = 14.7 Hz, 1H), 2.78 (d, $J$ = 14.2 Hz, 1H), 2.63 (dd, $J$ = 13.7, 8.8 Hz, 1H), 2.60 (d, $J$ = 14.7 Hz, 1H), 2.44 (d, $J$ = 14.2 Hz, 1H), 1.80 (dd, $J$ = 13.7, 1.5 Hz, 1H), 1.27 (s, 3H), and the other signals assigned to the menthyl moiety; HRMS m/z: Found, 662.3819 [$M^+$] (Calcd for $C_{40}H_{54}O_8$ 662.3866).

9. (a) In $^1H$ NMR spectra of the cycloadduct (**2a-d**), the characteristic vinyl signals assigned to two kinds of diastereomers were observed distinctly as two singlets: $^1H$ NMR (270 MHz, $CDCl_3$) δ: **2a**, 7.17, 7.04; **2b**, 6.94, 6.89; **2c**, 6.82, 6.84; **2d**, 6.25, 6.19. (b) The stereoselectivity of **2e** was determind by HPLC.

10. *Experimental procedure*: To a solution of (**1d**) (52.5 mg, 0.078 mmol) in $CH_2Cl_2$ (5 mL) was added 2,6-lutidine (0.025 mL, 0.21 mmol) and *t*-butyldimethysilyl triflate (TBSOTf) (0.05 mL, 0.21 mmol) under nitrogen atmosphere and the mixture was stirred at 20 °C for 16 h. The reaction mixture was poured into ice-cooled aqueous 2.5% $Na_2CO_3$ solution and extracted with $CH_2Cl_2$. The extracts were dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC on silica gel (hexane-EtOAc, 10 : 1) to give a pure sample (**2d**) (48.9 mg) in 96% yield at 97% conversion and with 70% d.e.
*Selected spectral data*; $^1H$ NMR (270 MHz, $CDCl_3$) for (**1d**), δ: 7.51 (s, 1H), 6.19 (s, 1H), 4.88 (s, 1H), 4.69 (s, 1H), 3.30 (d, $J$ = 15.1 Hz, 1H), 3.21 (d, $J$ = 15.1 Hz, 1H), 2.78 (d, $J$ = 15.6 Hz, 1H), 2.58 (d, $J$ = 15.6 Hz, 1H), 1.67 (s, 3H), 0.94 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H), and the other signals assigned to the menthyl moiety; HRMS m/z: Found, 672.4434 [$M^+$] (Calcd for $C_{39}H_{64}O_7Si$ 672.4421); for **1e**, δ: 7.53 (s, 1H), 6.16 (s, 1H), 4.89 (s, 1H), 4.70 (s, 1H), 3.06 (d, $J$ = 15.6 Hz, 1H), 2.83 (d, $J$ = 15.6 Hz, 1H), 2.60 (d, $J$ = 16.1 Hz, 1H), 2.48 (d, $J$ = 16.1 Hz, 1H), 1.56 (s, 3H), 0.95 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), and the other signals assigned to the 8-phenylmenthyl moiety; HRMS m/z: Found, 824.5060 [$M^+$] (Calcd for $C_{51}H_{72}O_7Si$ 824.5047); for the major isomer of **2d**, δ: 6.25 (s, 1H), 4.49 (dd, $J$ = 8.8, 1.5 Hz, 1H), 2.97 (d, $J$ = 14.2 Hz, 1H), 2.77 (s, 2H), 2.59 (dd, $J$ = 13.2, 8.8 Hz, 1H), 2.00 (d, $J$ = 14.2 Hz, 1H), 1.53 (dd, $J$ = 13.2, 1.5 Hz, 1H), 1.07 (s, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), and the other signals assigned to the menthyl moiety; HRMS m/z: Found, 672.4392 [$M^+$] (Calcd for $C_{39}H_{64}O_7Si$ 672.4421); for the major isomer of **2e**, δ: 6.14 (s, 1H), 4.46 (dd, $J$ = 8.8, 1.5 Hz, 1H), 2.69 (s, 1H), 2.51 (dd, $J$ = 13.8, 8.8 Hz, 1H), 2.43 (d, $J$ = 14.6 Hz, 1H), 2.16 (d, $J$ = 14.7 Hz, 1H), 1.73 (d, $J$ = 14.1 Hz, 1H), 1.50 (dd, $J$ = 13.9, 1.5 Hz, 1H), 1.23 (s, 3H), 0.95 (s, 9H), 0.17 (s, 6H), and the other signals assigned to the 8-phenylmenthyl moiety; HRMS m/z: Found, 809.4855 [$M^+$-Me] (Calcd for $C_{51}H_{72}O_7Si$ - $CH_3$ 809.4813).

11. *Trans*-bicyclo[3.3.0]octane system is about 6 kcal/mol less stable than the *cis*-form due to angle strain at the fusion points: S. Chang, D. McNally, S. Shary-Tehrany, S. M. J. Hickey, and R. H. Boyd, *J. Am. Chem. Soc.*, **92**, 3109 (1970).

Received, 24th July, 1997