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SYNTHESIS OF OPTICALLY ACTIVE BICYCLO[2.2.2]OCTANES. SUBSTITUTION EFFECT OF THE CYCLOHEXENONE RING ON THE SEQUENTIAL MICHAEL REACTION

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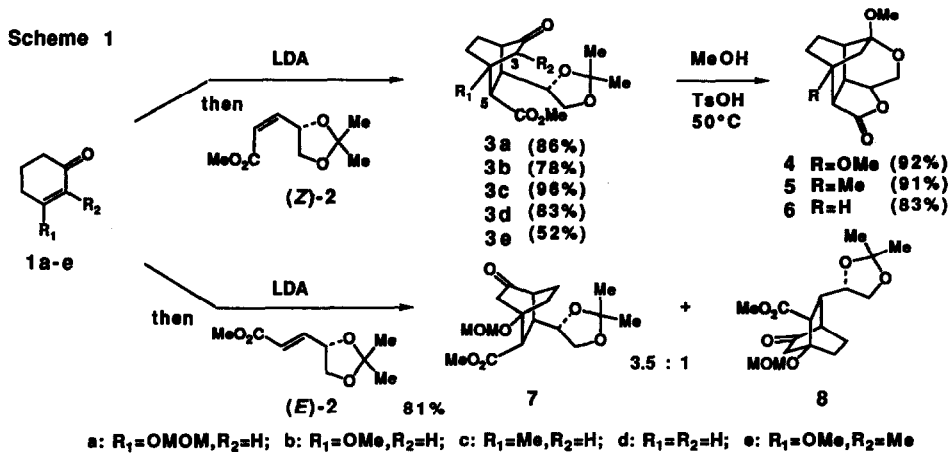
Key Words: sequential Michael reaction; bicyclo[2.2.2]octane derivative; methyl (*Z*)-(*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenate; methyl (*E*)-(*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenate; 2-cyclohexenone derivative.

Abstract: *Reactions of the cross-conjugated dienolate of 3-substituted 2-cyclohexenone **1b** and **1c**, 2-cyclohexenone (**1d**), and 2,3-disubstituted 2-cyclohexenone **1e** with methyl (S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenate (Z)-2 gave highly diastereoselectively **3b**, **3c**, **3d** and **3e**, respectively. The presence of a methyl group at C-6 on cyclohexenone ring caused the stereoselectivity to change completely, so that the reaction of the lithium enolate of **9** with (Z)-2 and with (E)-2 gave predominantly **11** and **12**, respectively.*

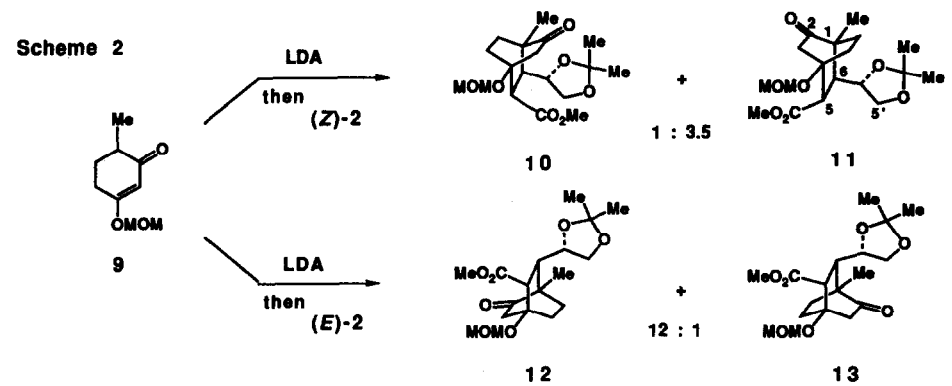
Bicyclo[2.2.2]octane derivatives are versatile intermediate in total synthesis of natural products having various types of carbon skeletons. Reactions of cross-conjugated dienolate anion with Michael acceptors have been found effective for synthesizing substituted bicyclo[2.2.2]octanes[1] as has also Diels-Alder reaction. In the previous communication, we have reported highly stereoselective reactions of the cross-conjugated dienolate of 3-methoxymethyloxy-2-cyclohexenone (**1a**) with methyl (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenate (*Z*)-**2** and (*E*)-**2** giving optically active bicyclo[2.2.2]octane derivative **3a** and **7/8**, respectively.[2,3] While conducting the synthesis of natural products using bicyclo[2.2.2]octanes as chiral building block,[4] assessment was made for the scope of application of this method. This paper discusses the effects of C-2, C-3 and C-6 substitutent groups of cyclohexenone ring on selectivity in this cyclization reaction.

Examination was initially made of the effects of C-3 substituent groups (R_1) of 2-cyclohexenone. The reactions of cross-conjugated dienolates, prepared from enone **1b** (R_1=OMe), **1c** (R_1=Me) and **1d** (R_1=H) and lithium diisopropylamide, with (*Z*)-**2**[5] in THF at low temperature (-78°C, 10 min; -42°C, 2 h; -42 to 25°C, 2 h; 25°C, 1 h) gave **3b**,[6] mp 142°C; $[\alpha]_D^{25}$ -35.0° (c 4.0, $CHCl_3$, **3c**, mp 113°C); $[\alpha]_D^{25}$ -28.0° (c 2.48, $CHCl_3$),[7] and **3d**, mp 60°C; $[\alpha]_D^{25}$ -24.3° (c 3.2, $CHCl_3$), as single isomers, respectively (Scheme 1). The stereochemistry of **3b-d** was determined by the formation of lactone ketal **4**, mp 131°C; $[\alpha]_D^{25}$ -9.4° (c 0.38, $CHCl_3$), **5**, mp 130°C; $[\alpha]_D^{25}$ +41.6° (c 0.57, $CHCl_3$),[3b] and **6**, mp 95°C; $[\alpha]_D^{25}$ 42.5° (c 0.7, $CHCl_3$), on treatment of them with a catalytic amount of *p*-toluenesulfonic acid in methanol. Groups at C-3 would thus appear not to have any effect on stereoselectivity in the cyclization reaction. The influence of C-2 substituent group was subsequently investigated. The reaction of the enolate of 2-methyl-3-methoxymethyloxy-2-cylohexenone (**1e**) with (*Z*)-**2** gave **3e**,[8] mp 130°C; $[\alpha]_D^{25}$ +12.7° (c 1.73, $CHCl_3$), as an only identified product.

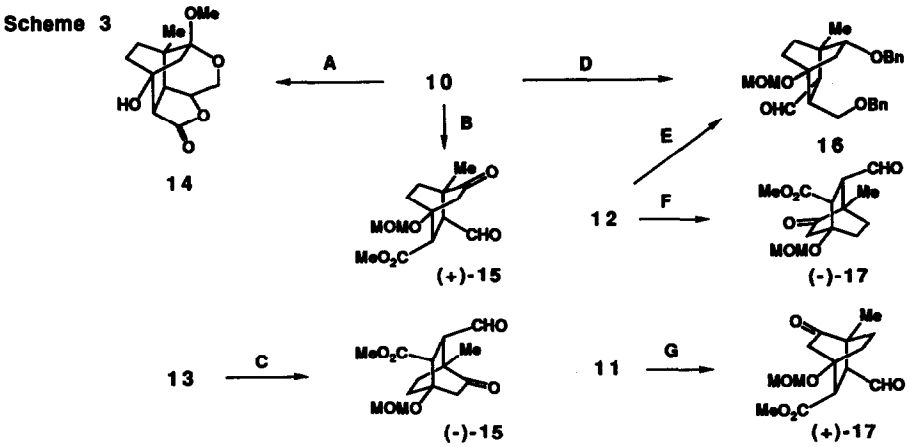


The stereoselectivity of this reaction is thus not affected by the methyl group of C-2.

However, the presence of a methyl group at the C-6 position of 2-cyclohexenone caused dramatic change in stereoselectivity. Reaction of the enolate of 6-methyl-3-methoxymethyloxy-2-cyclohexenone (**9**) with (*Z*)-**2** under similar reaction conditions afforded unexpected product **11**,[9] mp 101-4°C; $[\alpha]_D^{24}$ +121° (c 1.0, $CHCl_3$), as the major isomer accompanied with **10**,[10] mp 105-6°C; $[\alpha]_D^{24}$ -8.5° (c 1.0, $CHCl_3$), corresponding to **3** (Scheme 2). The ratio of **10** and **11** was 1:3.5.[11] The arrangement of the methoxycarbonyl group at C-5 and the 1,3-dioxolane moiety at C-6 in **11** was trans.[12] Reaction of the enolate of **9** with (*E*)-**2**[4c] gave predominantly **12**,[13,14] mp 65-6°C; $[\alpha]_D^{24}$ -85.0 (c 2.1, $CHCl_3$), corresponding to **8** with a small amount of exo adduct **13**,[15] mp 68-9°C; $[\alpha]_D^{24}$ -60.4 (c 1.0, $CHCl_3$), (**12**:**13**=12:1).[12] The configuration of **10** could be definitely determined by conversion to **14** as also shown for **3b-d**. Those of **11**, **12** and **13** were determined by their chemical correlation with **10** (Scheme 3). Acid hydrolysis of the acetonide group in **13** followed by $NaIO_4$ oxidation gave (-)-**15**, $[\alpha]_D^{24}$ -90° (c 1.0, $CHCl_3$), whose antipode (+)-**15**, $[\alpha]_D^{24}$ +103° (c 0.29, $CHCl_3$), was obtained from **10** in three steps. Keto ester **10** was transformed to dibenzylether **16** and it was also obtained from **12**.[4c] **12** was converted to keto aldehyde (-)-**17**, $[\alpha]_D^{24}$ -174° (c 1.0, $CHCl_3$), in three steps. Its enantiomer (+)-**17**, $[\alpha]_D^{24}$ +172° (c 1.0, $CHCl_3$), was obtained from **11** by similar treatment.



Scheme 3



Reagents: A. MeOH, *p*-TsOH, 70°C, 24 h, 91%; B. i) *t*-BuOK, THF-DMSO (2:1), 0°C, 15 min, 70%; ii) AcOH-H_2O (4:1), 25°C, 48 h; iii) $NaIO_4$, MeOH-5% $NaHCO_3$ (3:1), 0°C, 3 h, 40% (2 steps); C. i) 80%AcOH, 25°C, 24 h, 82%; ii) $NaIO_4$, MeOH-H_2O, 25°C, 2 h, 81%; D. i) L-selectride, THF, -78°C, 10 h, 96%; ii) $LiAlH_4$, THF, 25°C, 2 h, then 50°C, 1 h, 88%; iii) BnBr, NaH, DMF, 25°C, 6 h, 96%; iv) 80%AcOH, 25°C, 4 h, 76%; v) $NaIO_4$, MeOH-H_2O (2:1), 0°C, 1.5 h, 92%; vi) NaOH, EtOH, 25°C, 2 h, 87%; E. i) $LiAlH_4$, THF, 0°C 2 h, 25°C 12 h, 2α-OH (76%), 2β-OH (18%); ii) separation by silica gel column chromatography; iii) BnBr, NaH, DMF, 25°C, 7 h, 99%; iv) 80%AcOH, 25°C, 24 h, 83%; v) $NaIO_4$, MeOH-H_2O (2:1), 0°C, 1.5 h, 92%; F. i) 80%AcOH, 25°C, 48 h; ii) $NaIO_4$, MeOH-H_2O, 25°C, 1.5 h, 57% (2 steps); G. i) 80%AcOH, 25°C, 24 h, 71%; ii) $NaIO_4$, MeOH-H_2O, 25°C, 1.5 h, 84%

Stereoselectivty in the reactions of **1** with (*Z*)-**2** and with (*E*)-**2** can be explained by considering transition state **A** leading to **3** and **B** leading to **7**, respectively, as shown in Figure 1. In both states, the dienolate of **1** approaches **2**, which has a stable conformation (*Z*)-**2A** or (*E*)-**2A**, from the less hindered side with coordination between the lithium cation of dienolate **1** and the carbonyl oxygen of **2**. The reaction of **9** with (*E*)-**2** apparently proceeds *via* transition state **D** (Figure 2). In this case, transition state **C** corresponding to **B** is disfavored since there is steric repulsion between the newly introduced methyl group at C-6 and allylic oxygen. The mechanism for the formation of **11** from **9** and (*Z*)-**2** is not clear, but the route shown in Figure 3 appears to have a likely possibility. In this case, transition state **E** (corresponding to **C**) is superior to **F** (corresponding to **D**), because there is strong steric repulsion between the methoxycarbonyl group and allylic oxygen in (*Z*)-**2B**. Following the first Michael addition,[16] the C-C bond between C-5 and C-6 in **i** rotated to form **ii** which subsequently underwent the second Michael addition.

Fig. 1

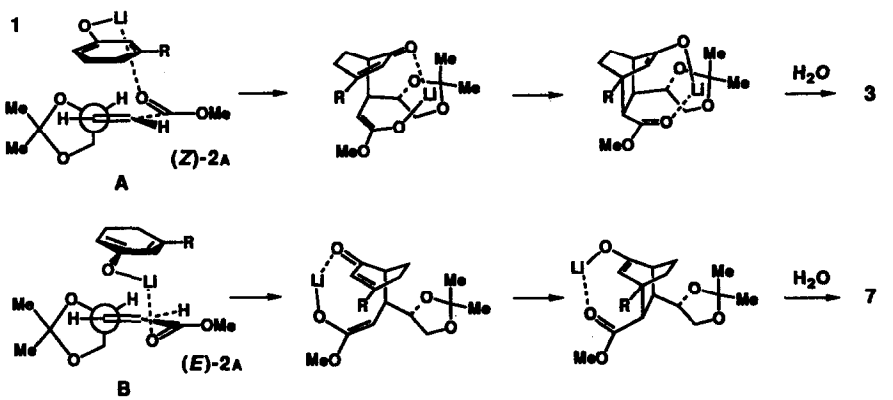


Fig. 2

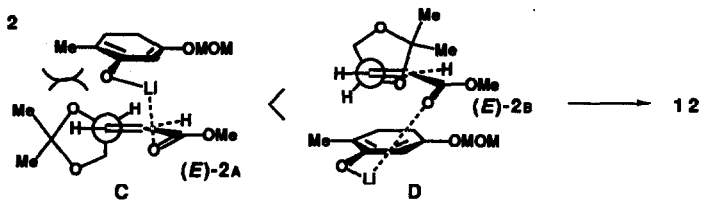
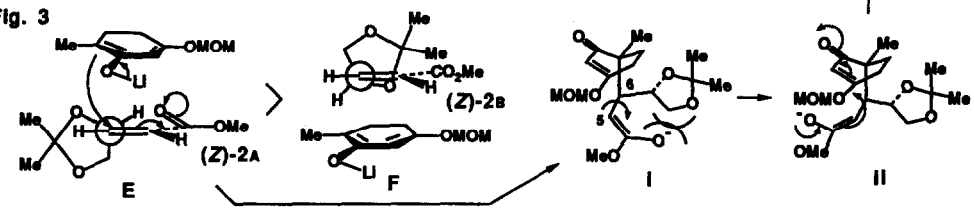


Fig. 3



In summary, the stereoselectivity of sequential Michael reactions of the enolate of 2-cyclohexenones with (*S*)-4,5-di-*O*-isopropylidenepent-2-enoate (*Z*)-**2** and with (*E*)-**2** is not affected by 2- or 3-substituent on the cyclohexenone ring, but is strongly influenced by 6-substituent. Bicyclo[2.2.2]octanes **3**, **7**, **11** and **12** thus obtained should be useful chiral building blocks for synthesizing natural products.

References and Notes

1. a) Lee, R. A. *Tetrahedron Lett.* **1973**, 3333. b) Hagiwara, H.; Nakayama, K.; Uda, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3769. c) White, K. B.; Reusch, W. *Tetrahedron* **1978**, *34*, 2439. d) Spitzner, D. *Tetrahedron Lett.* **1978**, 3349. *Angew. Chem.* **1978**, *90*, 301. *Tetrahedron Lett.* **1989**, *30*, 3349. e) White, K. B.; Reusch, W. *Tetrahedron* **1978**, *34*, 2439. f) Gibbons, E. G. *J. Org. Chem.* **1980**, *45*, 1541. *J. Am. Chem. Soc.* **1982**, *104*, 1767. g) Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1981**, *22*, 591. h) Nagaoka, H.; Ohsawa, K.; Takata, T.; Yamada, Y. *Tetrahedron Lett.*, **1984**, *25*, 5389. i) Spitzner, D.; Swoboda, H. *Tetrahedron Lett.* **1986**, 27, 1281. j) Schinzer, D.; Kalesse, M. *Tetrahedron Lett.* **1991**, *32*, 4691.
2. Nagaoka, H.; Kobayashi, K.; Matsui, T.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 2021.
3. Compounds **3a** and **7** were used as starting material in the total synthesis of (-)-sanadaol and (+)-sanadaol, respectively.[4a]
4. a) Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1988**, *29*, 5945; b) Iwashima, M.;Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1992**, *33*, 81; c) Nagaoka, H.; Shibuya, K.; Yamada, Y. *Tetrahedron Lett.*, in press.
5. a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. b) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009.
6. All new compounds have fully been characterized by IR, ^{1}H-NMR (400 MHz or 300 MHz), and high resolution mass spectroscopy and/or combustion analysis.
7. This compound was used as a starting material in total synthesis of fuscol.[4b]
8. Configuration of the methyl group at C-3 was determined by ^{1}H-NMR analysis. W-Shape long range coupling can be seen between H at C-3 (2.65 ppm, dq, *J*=0.93, 7.1 Hz) and H at C-5 (3.18 ppm, dd, *J*=0.93, 10.7 Hz).
9. Compound **11** was isolated from the mixture by recrystallization from ethyl acetate-ether.
10. Minor isomer **10** used for spectral data and chemical transformation was obtained by the following procedure: i) reduction of the mixture of **10** and **11** with L-selectride in THF at -78°C; ii) separation of the resulting alcohols by silica gel column chromatography [eluted with hexane-ether (1:1)]; and iii) oxidation with PDC and 4Å molecular seaves.
11. The ratio was determined by ^{1}H-NMR analysis.
12. The trans configuration was indicated by NOE correlation between the methine proton at C-5 (2.75 ppm, dd, *J*=1.8, 8.0 Hz) and one of the methylene proton at C-5'(3.65 ppm, t, *J*=8.3 Hz).
13. Compound **12** was isolated from the mixture by recrystallization from ether.
14. Compound **12** was used as a starting material in the total synthesis of upial.[4c]
15. Minor isomer **13** used for spectral data and chemical transformation was obtained by the similar procedure as described for **10**.[10]
16. Clear explanation why this reaction proceeded *via* nonchelation control was not found so far.

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