Radical-Based Synthesis of Terpenoids. Stereoselectivity in the Trapping of Radicals from Cyclization of 3-(1-Ethoxy-2-haloethoxy)cyclohexenes

Hajime Nagano,* Keiko Yamada, Noriko Hazeki, Yukie Mori,
and Tsuneo Hirano
Department of Chemistry, Faculty of Science, Ochanomizu University,
Otsuka, Bunkyo-ku, Tokyo 112
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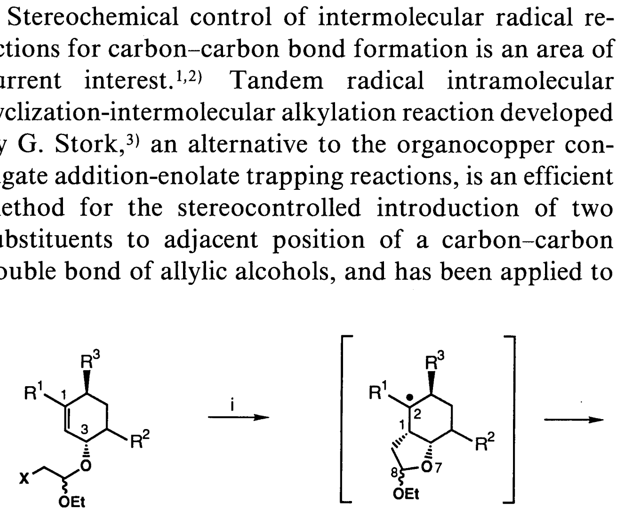
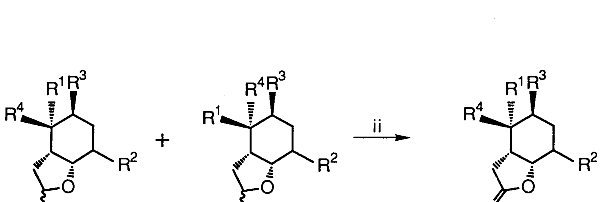
Stereoselectivity in the intermolecular trapping of the bicyclic radical intermediates from cyclization of 3-(1-ethoxy-2-haloethoxy)cyclohexenes with methyl acrylate was found to be affected remarkably by the conformation of the radical intermediates. The optimized conformers of 8-methoxy-7-oxabicyclo[4.3.0]non-2-yl radicals, models for the radical intermediates, were obtained by PM3 RHF molecular orbital calculations, and the stereoselectivity was analyzed in detail.

Stereochemical control of intermolecular radical reactions for carbon–carbon bond formation is an area of current interest.[1,2] Tandem radical intramolecular cyclization-intermolecular alkylation reaction developed by G. Stork,[3] an alternative to the organocopper conjugate addition-enolate trapping reactions, is an efficient method for the stereocontrolled introduction of two substituents to adjacent position of a carbon–carbon double bond of allylic alcohols, and has been applied to natural product synthesis.[4,5] Stork and Sher have reported that the regio- and stereoselective cyclization of 3-(1-ethoxy-2-haloethoxy)cyclohexenes (**1**) and 3-(1-ethoxy-2-iodoethoxy)-1-methylcyclohexene (**2**) followed by trapping of the *cis*-fused bicyclic radical intermediates **6** and **7** with *t*-butyl isocyanide or electron-deficient olefins (CH_2=CH–EWG; EWG=CO_2Me, CN, $COCH_3$, etc.) gave **11a** and **12a** (R^4=CN) as the major products, respectively (Scheme 1).[3b)] The stereochemistry of the second step is controlled by the cup shape of the *cis*-fused bicyclic radical intermediates **6** and **7**. In the course of our radical-based synthesis of terpenoids[4,6)] we found that the stereoselectivity was affected remarkably by the conformation of the radical intermediates. We now report the detailed conformational analysis of the radical intermediates **6**—**10** by the cyclization of 3-(1-ethoxy-2-haloethoxy)cyclohexenes **1**—**5**, and the conformational effects on the stereoselectivity in the intermolecular trapping reaction of the radical intermediates with methyl acrylate.

Compound **3** was prepared from (+)-*cis*-carvyl acetate (**16**) (Scheme 2). Allylic oxidation of **16** with chromium (VI) oxide–3,5-dimethylpyrazole[7)] gave the enone **17** with



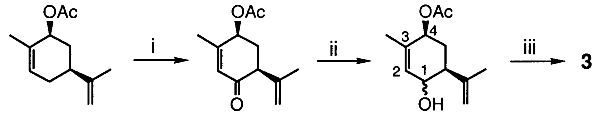
1	R^1=R^2=R^3=H, X=Br or I	**6**	R^1=R^2=R^3=H
2	R^1=Me, R^2=R^3=H, X=I	**7**	R^1=Me, R^2=R^3=H
3	R^1=Me, R^2=β-C(=CH_2)Me, R^3=OAc, X=Br	**8**	R^1=Me, R^2=β-C(=CH_2)Me, R^3=OAc
4	R^1=Me, R^2=β-CH_2Ph, R^3=H, X=I	**9**	R^1=Me, R^2=β-CH_2Ph, R^3=H
5	R^1=Me, R^2=α-CH_2OMEM, R^3=H, X=Br	**10**	R^1=Me, R^2=α-CH_2OMEM, R^3=H



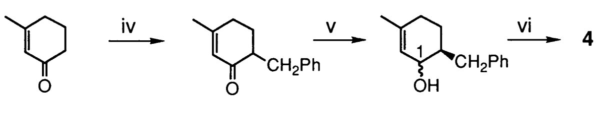
11a - 15a **11b, 12b, 15b** **22, 23**

11a, 11b	R^1=R^2=R^3=H, R^4=CN or CH_2CH_2EWG
12a, 12b	R^1=Me, R^2=R^3=H, R^4=CN or $CH_2CH_2CO_2Me$
13a, 22	R^1=Me, R^2=β-C(=CH_2)Me, R^3=OAc, R^4=$CH_2CH_2CO_2Me$
14a, 23	R^1=Me, R^2=β-CH_2Ph, R^3=H, R^4=$CH_2CH_2CO_2Me$
15a, 15b	R^1=Me, R^2=α-CH_2OMEM, R^3=H, R^4=$CH_2CH_2CO_2Me$ or CH_2CH_2CN

Scheme 1. Reagents and Conditions: i, Bu_3SnCl (0.2 equiv), $NaBH_3CN$ (2 equiv), azobisisobutyronitrile (0.2 equiv), CH_2=$CHCO_2Me$, CH_2=CHCN, or *t*-BuNC (10—25 equiv), *t*-BuOH, Ar, 80 °C; ii, Jones oxidation.



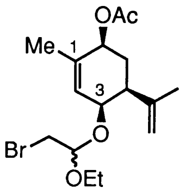
16 **17** **18** 1α-OH
18' 1β-OH



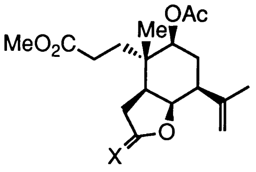
19 **20** **21** 1α-OH
21' 1β-OH

Scheme 2. Reagents and Conditions: i, CrO_3–3,5-dimethylpyrazole, −40 °C; ii, $NaBH_4$–$CeCl_3$; iii, CH_2=CHOEt, *N*-bromosuccinimide; iv, LiN(*i*-Pr)$_2$, $PhCH_2Br$, −40 °C; v, $LiAlH_4$, −78 °C; vi, CH_2=CHOEt, *N*-iodosuccinimide.

high purity.[8] Reduction of **17** with $NaBH_4$–$CeCl_3$[9] gave an inseparable mixture of the allylic alcohols **18** and **18′** in a ratio of 8 : 1. The stereochemistry of **18** and **18′** was determined by comparison of the ^1H NMR signals of 1-H and 2-H [**18**: δ=4.18 (br d, J=8 Hz, 1-H) and 5.63 (q, J=1.7 Hz, 2-H); **18′**: δ=4.13 (br s, 1-H) and 5.82 (d, J=5.4 Hz, 2-H)].[10] The mixture was treated with ethyl vinyl ether-*N*-bromosuccinimide to give an inseparable mixture of the bromo acetals **3** and **3′**. The bromo acetal **3** was submitted to the tandem radical reaction without further purification. Compound **4** was prepared from 3-methyl-2-cyclohexen-1-one (**19**). The kinetic enolate of **19** was treated with benzyl bromide to give the enone **20**.[11] Reduction of **20** with lithium aluminium hydride at −78 °C gave the allylic alcohols **21** and **21′** in a ratio of 6 : 1, which were separated by flash chromatography. The stereochemistry of the allylic alcohols **21** and **21′** was determined by comparison of their ^1H NMR spectra [**21**(*trans*): δ=3.92 (m, 1-H) and 5.41 (br s, 2-H); **21′** (*cis*): δ=3.88 (br s, 1-H) and 5.88 (br s, 2-H)].[5,10] The allylic alcohol **21** was then transformed to the iodo acetal **4**.

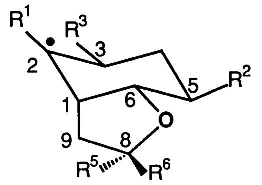


3'

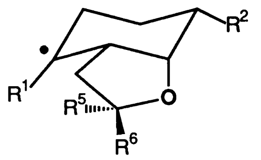


13' X=H, OH
22' X=O

In the work of Stork and Sher intermolecular trapping of **7** with *t*-butyl isocyanide gave **12a** (R^4=CN) and **12b** (R^4=CN) in a ratio of 12.4 : 1.[3b] In the trapping of **7** with methyl acrylate were obtained **12a** (R^4=$CH_2CH_2CO_2Me$) and **12b** (R^4=$CH_2CH_2CO_2Me$) in a ratio of 12.5 : 1 and in 67% yield. The tandem radical reaction of the bromo acetal **3** and the iodo acetal **4** in the presence of methyl acrylate gave exclusively **13a** and **14a** in 58% and 63% yields, respectively. The stereochemistry of the newly formed quaternary carbon center was assigned by the relative ease of access to the radical intermediates **7**, **8**, and **9**, and confirmed by the nuclear Overhauser enhancement (NOE) of the axial methine proton ar δ=4.96 (dd, J=11.2 and 4.4 Hz, C*H*OAc) on irradiation of the singlet methyl peak at δ=0.94 of the lactone **22** obtained by Jones oxidation of **13a**. In our previous synthesis of 1-*epi*-magydardienediol using the tandem radical reaction of the *cis*-bromo acetal **5**, however, the intermolecular trapping reaction proceeded less stereoselectively. The trapping of **10** with methyl acrylate gave **15a** (R^4=$CH_2CH_2CO_2Me$) and **15b** (R^4=$CH_2CH_2CO_2Me$) in a ratio of 4 : 1 and that with acrylonitrile gave **15a** (R^4=CH_2CH_2CN) and **15b** (R^4=CH_2CH_2CN) in a ratio of 2 : 1.[4]



7A—9A, 24A—27A



7B, 10B, 24B—27B

7A, 7B	R^1=Me, R^2=R^3=H, R^5, R^6=H, OEt
8A	R^1=Me, R^2=β-C(=CH_2)CH_3, R^3=OAc, R^5, R^6=H, OEt
9A	R^1=Me, R^2=β-CH_2Ph, R^3=H, R^5, R^6=H, OEt
10B	R^1=Me, R^2=α-CH_2OMEM, R^3=H, R^5, R^6=H, OEt
24A, 24B	R^1=Me, R^2=R^3=R^5=H, R^6=OMe
25A, 25B	R^1=Me, R^2=R^3=R^6=H, R^5=OMe
26A, 26B	R^1=R^2=R^3=R^5=H, R^6=OMe
27A, 27B	R^1=R^2=R^3=R^6=H, R^5=OMe

The remarkable difference of stereoselectivity in the tandem radical reaction of **2**—**5** is attributable to the conformation of the bicyclic radical intermediates **7**—**10**. The intermediates **8** and **9** adopt the conformers **8A** and **9A**, respectively, in which all the substituents occupy equatorial positions, while the intermediate **10** adopts the conformer **10B** in which the CH_2OMEM group (MEM=$CH_2OCH_2CH_2OCH_3$) occupies an equatorial position. The optimized structure of conformers **24A**, **24B**, **25A**, and **25B** of 8-methoxy-2-methyl-7-oxabicyclo[4.3.0]non-2-yl radical, a model for the radicals **7**—**10**, was obtained by PM3 RHF molecular orbital calculations (Table 1 and Fig. 1).[#] Methoxyl substituent was used instead of ethoxyl group for the facility of calculations. From inspection of the optimized structure of the conformers **24A** and **25A**, approach of methyl acrylate to the concave face of the bicyclic radical intermediates **8A** and **9A** may by strictly prohibited by the steric hindrance of the pseudo-axial C1–C9 and C3–H(3α) bonds adjacent to the planar radical center (C2), and the trapping with methyl acrylate proceeded exclusively on the convex face of **8A** and **9A** to give **13a** and **14a**, respectively. In the trapping of **8**, axial attack proceeded exclusively even in the presence of the equatorial acetoxyl group which would direct the reaction towards equatorial attack.[1] The C1–C9 and C3–H(3α) bonds of **10B** occupy pseudo-equatorial positions and the trapping with methyl acrylate may be allowed to proceed on the concave face (i.e., equatorial attack). Furthermore, the shielding of the convex face of **10B** by the pseudo-axial C3–H(3β) bond may cause the decrease of the proportion of axial attack.

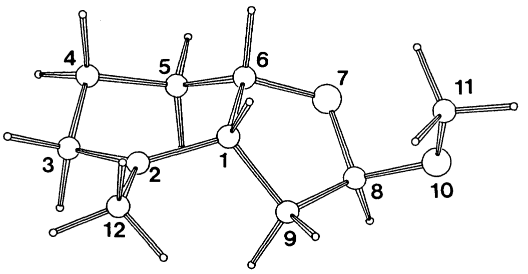
The heats of formation ($\Delta H_f{}^\circ{}_{298}$) of the conformers **24A**, **24B**, **25A**, and **25B** were calculated by PM3 RHF method and the small energy differences between **24A**

[#] PM3 RHF molecular orbital calculations were performed on a HITAC M880 with MOPAC package Ver. 6.01 converted from Ver. 6 of J. J. P. Stewart, QCPE 455 by Tsuneo Hirano, Ochanomizu University.

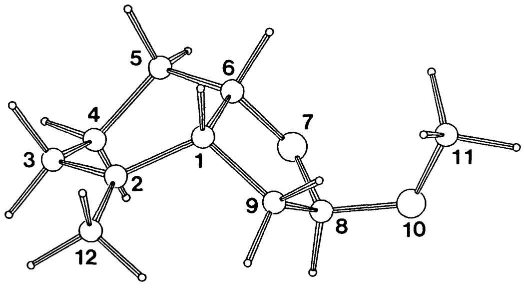
Table 1. Optimized Angles (deg) and Heats of Formation ($\Delta H_\mathrm{f}{}^\circ{}_{298}$; kcal mol^{-1})[a] of Radicals **24A**—**27B**

	24A	**24B**	**25A**	**25B**	**26A**	**26B**	**27A**	**27B**
C3-C2-C1-C9[b]	108.5	131.3	108.4	124.3	125.5	126.9	126.1	116.7
C3-C2-C1-H(1)[b]	−131.6	−108.4	−131.8	−116.0	−115.0	−113.1	−114.4	−123.8
C1-C9/P[c]	118.8	135.2	118.6	130.2	131.6	131.6	132.2	123.7
C1-H(1)/P[c]	133.9	114.1	133.9	119.2	118.5	117.4	117.7	125.9
H(3α)/P[c]	109.0	153.5	108.9	151.1	120.2	144.9	120.7	146.0
H(3β)/P[c]	148.4	106.9	148.6	108.5	133.9	108.4	133.3	110.9
$\Delta H_\mathrm{f}{}^\circ{}_{298}$	−86.49	−86.24	−86.61	−85.15	−76.09	−75.74	−75.98	−74.77

a) 1 kcal=4.184 J. b) Dihedral angle. c) Angle between the bond and P (P: the least-squares plane of C1, C2, C3, and C12 for **24A**—**25B** and that of C1, C2, C3, and H(2) for **26A**—**27B**).



24A



24B

Fig. 1. PM3 RHF-Optimized structure of conformers **24A** and **24B** (C2: radical center).

($\Delta H_\mathrm{f}{}^\circ{}_{298}$ −86.49 kcal mol^{-1}; 1 cal=4.184 J) and **24B** (−86.24) and between **25A** (−86.61) and **25B** (−85.15) were shown. As compared with the low conformational inversion barrier of *cis*-hydrindans,[12] the inversion barrier of **7** is expected to be sufficiently low, and **7** exists as a rapidly interconverting equilibrium mixture of **7A** and **7B** at the reaction temperature (80 °C). The intermolecular trapping of **7** may proceed through both **7A** and **7B**;[13] the former gives exclusively **12a** and the latter gives both the diastereomers **12a** and **12b** in a ratio similar to that of **10**. Thus the 12.5 : 1 stereoselectivity in the trapping reaction of **7** lying between the stereoselectivity of **8** and **9** and that of **10** is well accounted for by the small energy difference between **7A** and **7B** and their rapid interconversion.

In the case of 8-methoxy-7-oxabicyclo[4.3.0]non-2-yl radical, a model for the bicyclic radical **6**, the corresponding conformers **26A**, **26B**, **27A**, and **27B** were obtained by PM3 RHF optimization (Table 1). The angles between the least-squares plane of C1, C2, C3, and H(2) and the C1–C9 bond of **26A** (131.6°) and **27A** (132.2°) are larger than those of **24A** (118.8°) and **25A** (118.6°), i.e, the C1–C9 bond of **26A** and **27A** occupies a pseudo-equatorial position. The reported stereoselectivity in the trapping of **6** (7.5 : 1 with *t*-butyl isocyanide and 8.8 : 1 with acrylonitrile)[3b] which is slightly lower than that of **7** may by explained by the decrease of steric hindrance due to the C1–C9 bond in **6**.

Experimental

IR spectra were taken on a JASCO A-3 spectrometer for thin-layer films on sodium chloride plates. ^{1}H NMR spectra were recorded on a JEOL GX-270 (270 MHz) spectrometer with chloroform-*d* as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on the same instrument (67.8 MHz) with chloroform-*d* as internal standard. Mass spectra were obtained by direct introduction on a JEOL DX-300 mass spectrometer using electron impact (EI) mode (70 eV). Accurate mass measurements were recorded on the mass spectrometer. Precoated Merck Kiesel-gel 60 F_{254} was used for general analytical purposes and silica gel (Wakogel C-300) was used for flash chromatography.

(4*S*,6*S*)-4-Acetoxy-6-isopropenyl-3-methyl-2-cyclohexen-1-one (17). To a suspension of chromium(VI) oxide (14.9 g) in dry dichloromethane (80 ml) cooled to −40 °C was added 3,5-dimethylpyrazole (14.3 g), and the mixture was stirred at this temperature for 20 min under nitrogen. A solution of (+)-*cis*-carvyl acetate (**16**) (1.94 g) in dry dichloromethane (15 ml) was then added, and the mixture was stirred at −40 °C for 4.5 h. Diethyl ether (100 ml) was added and the precipitate formed was filtered out. The filtrate was then washed successively with aqueous sodium hydrogencarbonate and saturated brine, and dried over anhydrous sodium sulfate. The crude product was chromatographed on silica gel (200 g). Elution with hexane–diethyl ether (15 : 1) gave the unreacted starting material **16** (0.44 g, 23% yield), and elution with hexane–diethyl ether (6 : 1) gave **17** (0.54 g, 26%) with high purity. Spectral data of the enone **17** were identical with those of its enantiomer reported in Ref. 8. Allylic oxidation of (+)-*cis*-carvyl acetate (**16**) with *t*-butyl chromate following the procedures reported in Ref. 8 gave the enone **17** in higher yield, but its purification was difficult.

(1*R*,4*S*,6*S*)-4-Acetoxy-6-isopropenyl-3-methyl-2-cyclohexen-1-ol (18). To a solution of the enone **17** (452 mg) in tetrahydrofuran (24 ml) was added a solution of cerium(III) chloride hexahydrate (928 mg) in methanol (4 ml). The solution was then cooled to −78 °C and sodium borohydride (169 mg) was added. The mixture was then stirred at this temperature for 4 h, and then warmed to 0 °C. Dilute hydrochloric acid (2 mol dm^{-3}; 15 ml) was added, and then the solution was concentrated under reduced pressure to give a residue, which was extracted three times with dichloromethane. The combined organic layers were washed with water and then with saturated brine, and dried over anhydrous sodium sulfate. The crude product was chromatographed on silica gel (25 g) (eluent: hexane–ethyl acetate 6 : 1) to give an inseparable mixture of the allylic alcohols **18** and **18′** as an oil (384 mg, 84% yield). The 8 : 1 diastereomer ratio was determined by the integration of its ^{1}H NMR spectrum.

18 and **18′**: IR 3430, 3080, 1740, 1645, 1455, 1440, 1372, 1240, 1030, 970, 920, and 895 cm^{-1}; MS *m*/*z* 210 (M$^+$, 0.2), 168(0.9), 150(12), 142(27), 100(100), and 71(25). Found: *m*/*z* 210.1305. Calcd for $C_{12}H_{18}O_3$: M, 210.1256.

18: ^{1}H NMR δ=5.63 (1H, q, J=1.7 Hz, 2-H), 5.46 (1H, $W_{1/2}$=21 Hz, 4-H), 4.92 (1H, q, J=1.7 Hz, =CH_2), 4.90 (1H, br s, =CH_2), 4.18 (1H, br d, J=8.3 Hz, 1-H), 2.08 (3H, s, CH_3CO_2), 1.73 (3H, br s, =CCH_3), and 1.68 (3H, br s, =CCH_3); ^{13}C NMR: δ=170.75, 144.41, 135.09, 129.62, 72.54, 68.38, 50.46, 32.75, 21.08, 19.01, and 18.59.

18′: ^{1}H NMR δ=5.82 (1H, d, J=5.4 Hz, 2-H), 5.35 (1H, dd, J=10.5 and 6.0 Hz, 4-H), 5.02 (1H, br s, =CH_2), 4.79 (1H, br s, =CH_2), 4.13 (1H, br s, 1-H), 2.10 (3H, s, CH_3CO_2), and 1.82 (6H, s, =CCH_3); ^{13}C NMR: δ=170.81, 145.15, 138.55, 126.39, 72.70, 63.40, 44.54, 26.99, 22.21, and 18.69.

(3*R*,4*S*,6*S*)-6-Acetoxy-3-[(1ξ)-2-bromo-1-ethoxyethoxy]-4-isopropenyl-1-methylcyclohexene (3). To a solution of the allylic alcohols **18** and **18′** (180 mg) in dry dichloromethane (4 ml) cooled to −40 °C were added ethyl vinyl ether (0.42 ml) and *N*-bromosuccinimide (458 mg) and the mixture was stirred at this temperature for 5 h. Aqueous sodium hydroxide (5%; 10 ml) was then added, and the product was extracted three times with dichloromethane. The combined organic layers were washed with water and then with saturated brine, and dried over anhydrous sodium sulfate. The crude product was chromatographed on silica gel (17 g) (eluent: hexane–ethyl acetate 20 : 1) to give an inseparable mixture of **3** and **3′** (285 mg, 92% yield) in a ratio of 8 : 1.

3 and **3′**: An oil; IR 3080, 1740, 1645, 1440, 1375, 1240, 1025, 922, and 897 cm^{-1}; MS *m*/*z* 302 (M$^+$−CH_3CO_2H, 0.8), 300 (M$^+$−CH_3CO_2H, 0.8), 294(4), 292(4), 255(34), 153(90), 151(100), 150(59), 149(48), 142(90), 133(52), 125(97), 123(97), 100(64), 91(34), and 72(47). Found: *m*/*z* 300.0680. Calcd for $C_{14}H_{21}BrO_2$: M−CH_3CO_2H, 300.0725.

3: ^{1}H NMR δ=5.62 (1H, m, 2-H), 5.42 (1H, br s, 6-H), 4.87 (2H, m, =CH_2), [4.79 (t, J=5.6 Hz) and 4.70 (t, J=5.4 Hz) (1H, $OCH(OEt)$)], 4.21 (1H, m, 3-H), 3.8—3.55 (2H, m, OCH_2CH_3), 3.33 (2H, m, CH_2Br), 2.41 (1H, m, 4-H), 2.07 (3H, s, CH_3CO_2), 1.75 (3H, s, =CCH_3), 1.68 (3H, s, =CCH_3), and [1.25 and 1.19 (3H, t, J=7.1 Hz, OCH_2CH_3)].

6-Benzyl-3-methyl-2-cyclohexen-1-one (20). To a solution of lithium diisopropylamide, prepared from butyllithium (1.6 mol dm^{-3} in hexane; 7.5 ml) and diisopropylamine (1.7 ml) in dry tetrahydrofuran (25 ml), cooled to −78 °C was added dropwise a solution of 3-methyl-2-cyclohexen-1-one (**19**) (1.15 ml) in dry tetrahydrofuran (3 ml). The solution was stirred at −78 °C for 30 min, and a solution of benzyl bromide (1.45 ml) in tetrahydrofuran (3 ml) was added dropwise. The mixture was stirred at −78 °C for 10 min and then at −40 °C overnight. Saturated aqueous ammonium chloride (50 ml) was added and the mixture was warmed to room temperature. The aqueous layer was extracted several times with diethyl ether. The combined organic layers were washed with water and then with saturated brine, and dried over anhydrous sodium sulfate. Flash chromatography of the extract (SiO_2, 200 g; eluent: hexane–ethyl acetate 30 : 1) gave **20** (2.04 g, 95% yield), an oil; IR 3040, 1670, 1640, 1605, 1500, 1460, 1435, 1385, 1215, 743, and 703 cm^{-1}; ^{1}H NMR δ=7.3—7.15 (5H, m, Ph), 5.90 (1H, br s, 2-H), 3.36 (1H, m, 6-H), 2.46 (2H, m, CH_2Ph), 2.25 (1H, dd, J=6.3 and 5.6 Hz, 4-H), and 1.94 (3H, s, 3-CH_3); ^{13}C NMR δ=200.53, 161.73, 140.19, 129.23, 128.38, 126.35, 126.35, 126.08, 47.35, 35.41, 30.46, 26.93, and 24.19; MS *m*/*z* 200 (M$^+$, 71), 185 (M$^+$−CH_3, 7), 109 (M$^+$−CH_2Ph, 100), 91 (CH_2Ph, 81), and 82(95). Found: *m*/*z* 200.1181. Calcd for $C_{14}H_{16}O$: M, 200.1201.

***trans*-6-Benzyl-3-methyl-2-cyclohexen-1-ol (21).** To a suspension of lithium aluminium hydride (209 mg) in dry diethyl ether (20 ml) cooled to −78 °C was added a solution of the enone **20** (501 mg) in dry diethyl ether (5 ml). The mixture was stirred at this temperature for 3 h under nitrogen. After an excess of lithium aluminium hydride was decomposed the product was extracted with diethyl ether and chromatographed on silica gel (30 g). Elution with hexane–ethyl acetate (40 : 1) gave the *trans*-allylic alcohol **21** (376 mg, 74% yield) and *cis*-allylic alcohol **21′** (59 mg, 12% yield).

21: An oil; IR 3400, 3040, 1500, 1458, 1038, 1008, 740, and 700 cm^{-1}; ^{1}H NMR δ=7.3—7.15 (5H, m, Ph), 5.41 (1H, br s, 2-H), 3.92 (1H, m, 1-H), 3.02 (1H, dd, J=13.4 and 4.6 Hz, CH_2Ph), 2.41 (1H, dd, J=13.4 and 8.8 Hz, CH_2Ph), 1.88 (2H, m, 4-H), and 1.68 (3H, s, 3-CH_3); ^{13}C NMR δ=140.73, 137.87, 129.27, 128.29, 125.90, 124.35, 71.33, 43.75, 38.61, 29.23, 24.91, and 23.23; MS *m*/*z* 202 (M$^+$, 26), 187 (M$^+$−CH_3, 25), 184 (M$^+$−H_2O, 21), 124(20), 111(34), 110(67), 93(69), 91 (CH_2Ph, 100), 84(84), and 77(29). Found: *m*/*z* 202.1356. Calcd for $C_{14}H_{18}O$: M, 202.1358.

21′: An oil; ^{1}H NMR δ=7.24 (5H, m, Ph), 5.58 (1H, br s, 2-H), 3.88 (1H, br s, 1-H), 2.83 (1H, dd, J=13.7 and 7.6 Hz, CH_2Ph), 2.59 (1H, dd, J=13.7 and 7.6 Hz, CH_2Ph), 1.96 (2H, m, 4-H), 1.76 (1H, m, 6-H), 1.69 (3H, s, 3-CH_3), and 1.53 (2H, m, 5-H).

***trans*-4-Benzyl-3-[(1ξ)-1-ethoxy-2-iodoethoxy]-1-methylcyclohexene (4).** The *trans*-allylic alcohol **22** (150 mg) was treated with ethyl vinyl ether (0.25 ml) and *N*-iodosuccinimide (254 mg) in dichloromethane (10 ml) at −40 °C. Flash chromatography of the crude product (eluent: hexane–ethyl acetate 50 : 1) gave the iodo acetal **4** in quantitative yield.

4: An oil; IR 3030, 1500, 1455, 1100, 1055, 1015, 745, and 700 cm^{-1}; ^{1}H NMR δ=7.3—7.15 (5H, m, Ph), 5.49 (1H, br s, 2-H), [4.70 (dd, J=5.1 and 5.1 Hz) and 4.62 (dd, J=5.46 and 5.6 Hz), (1H, $OCH(OEt)$)], [3.87 and 3.80 (1H, m, 3-H)], 3.70—3.47 (2H, m, OCH_2CH_3), 3.19 (2H, m, CH_2I), 2.94 (1H, m, CH_2Ph), [2.39 and 2.34 (1H, t, J=8.5 Hz, CH_2Ph)], 1.71 (3H, s, 1-CH_3), and [1.20 and 1.18 (3H, t, J=7.1 Hz, CH_2CH_3)]; MS *m*/*z* 354 (M$^+$−CH_3CH_2OH, 0.1) 273 (M$^+$−I, 0.4), 201 (M$^+$−$CH(OEt)CH_2I$, 73), 199 ($CH(OEt)CH_2I$, 52), 185 (M$^+$−$OCH(OEt)CH_2I$, 24), 171(34), 93(34), and 91 (CH_2Ph, 100). Found: *m*/*z* 354.0481. Calcd for $C_{16}H_{19}IO$: M−CH_3CH_2OH, 354.0480.

Methyl (1*S,2*R**,6*R**)-3-[(8ξ)-8-Ethoxy-2-methyl-7-oxabicyclo[4.3.0]non-2-yl]propionate (12a) and Methyl (1*S**,2*S**,**

6*R)-3-[(8ξ)-8-Ethoxy-2-methyl-7-oxabicyclo[4.3.0]non-2-yl]propionate (12b).** A mixture of the iodo acetal **2** (307 mg), tributyltin chloride (30 μl), sodium cyanotrihydroborate (138 mg), azobisisobutyronitrile (22 mg), and methyl acrylate (0.9 ml) in *t*-butyl alcohol (28 ml) was stirred at 80 °C for 1.5 h under argon, and was then washed successively with 3% aqueous ammonia (50 ml) and saturated brine (5 ml). The aqueous layer was further washed with dichloromethane three times. The combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (25 g). Elution with hexane–ethyl acetate 20 : 1 (200 ml) and 10 : 1 (300 ml) gave an inseparable mixture of **12a** and **12b** (179 mg, 67% yield) as an oil; IR 1743, 1470, 1440, 1375, 1195, 1170, 1115, 1043, 1018, and 878 cm^{-1}.

12a: ^{1}H NMR δ=[5.14 (0.5H, dd, J=5.4 and 5.4 Hz, OCH(OEt)) and 5.08 (0.5H, dd, J=5.4 and 1.2 Hz, OCH(OEt))], [4.23 (0.5H, m, 6-H) and 4.08 (0.5H, ddd, J=11.2, 6.1, and 6.1 Hz, 6-H)], 3.67 (3H, s, CO$_2$CH$_3$), 3.75 (1H, m, CH_2CH$_3$), 3.44 (1H, m, CH_2CH$_3$), [1.201 and 1.197 (3H, t, J=7.1 Hz, CH$_2$CH_3)], and [0.87 and 0.84 (3H, s, 2-CH$_3$)]. The minor product **12b** showed the singlet signals of 2-CH$_3$ at δ=0.97 and 0.95. The 12.5 : 1 ratio of **12a** and **12b** was determined by the integration of the signals of 2-CH$_3$ in the ^{1}H NMR spectrum.

Methyl (1*R*,2*R*,3*S*,5*S*,6*S*)-3-[(8ξ)-3-Acetoxy-8-ethoxy-5-ispropenyl-2-methyl-7-oxabicyclo[4.3.0]non-2-yl]propionate (13a). A mixture of the bromo acetal **3** and **3′** (361 mg), tributyltin chloride (54 μl), sodium cyanotrihydroborate (316 mg), azobisisobutyronitrile (35 mg), and methyl acrylate (1.8 ml) in *t*-butyl alcohol (25 ml) was stirred at 80 °C for 2.5 h under argon. Tributyltin chloride (27 μl) was then added and the mixture was stirred at 80 °C overnight. Work-up as described above gave an oily product, which was chromatographed on silica gel (50 g). Elution with hexane–ethyl acetate (15 : 1) gave an inseparable mixture of **13a** and **13′** (212 mg, 58% yield), an oil; IR 3070, 1738, 1642, 1440, 1375, 1240, 1195, 1118, 1097, 1018, and 890 cm^{-1}; MS m/z 368 (M$^+$, 0.2), 322 (M$^+$$-CH_3CH_2$OH, 0.8), 262 (M$^+$$-CH_3CO_2H-CH_3CH_2$OH, 49), 227(53), 194(44), 175(75), 147(51), and 121(100). Found: m/z 262.1595. Calcd for C$_{16}$H$_{22}$O$_3$: M$-$C$_4$H$_{10}$O$_3$, 262.1567.

13a: ^{1}H NMR δ=5.10 (1H, m, OCH(OEt)), 4.86 (1H, d, J=1.5 Hz, =CH$_2$), 4.82 (1H, br s, =CH$_2$), 4.21 (0.5H, m, 6-H), 4.00 (0.5H, dd, J=10.7 and 6.3 Hz, 6-H), 3.77 (1H, m, 3-H), 3.67 (3H, s, CO$_2$CH$_3$), 3.39 (2H, m, OCH_2CH$_3$), 2.05 (3H, s, CH$_3$CO$_2$), 1.76 (3H, s, =CCH$_3$), [1.19 and 1.17 (3H, t, J=7.1 Hz, CH$_2$CH_3)], and [0.93 and 0.91 (3H, s, 2-CH$_3$)].

Methyl (1*R,2*R**,5*S**,6*S**)-3-[(8ξ)-6-Benzyl-8-ethoxy-2-methyl-7-oxabicyclo[4.3.0]non-2-yl]propionate (14a).** A mixture of the iode acetal **4** (208 mg), tributyltin chloride (15 μl), sodium cyanotrihydroborate (66 mg), azobisisobutyronitrile (9 mg), and methyl acrylate (0.47 ml) in *t*-butyl alcohol (15 ml) was stirred at 80 °C for 4 h under argon. Work-up as described above gave an oil, which was chromatographed on silica gel (15 g). Elution with hexane–ethyl acetate 30 : 1 (200 ml) and 20 : 1 (200 ml) gave **14a** (117 mg, 63% yield), an oil; IR 3030, 1740, 1605, 1500, 1455, 1375, 1190, 1165, 1013, 960, 875, 750, and 700 cm^{-1}; MS m/z 360 (M$^+$, 2), 329 (M$^+$$-CH_3$O, 2), 314 (M$^+$$-CH_3CH_2$OH, 6), 223(48), 222(41), 195(26), 181(26), 135(64), and 91 (CH$_2$Ph, 100). Found: m/z 360.2314. Calcd for C$_{22}$H$_{32}$O$_4$: M, 360.2300. The diastereomers of **14a** were partly separated by the flash chromatography.

14a (higher R_f): An oil; ^{1}H NMR δ=7.3—7.1 (5H, m, Ph), 5.13 (1H, d, J=5.1 Hz, OCH(OEt)), 3.93 (1H, dd, J=9.5 and 6.8 Hz, 6-H), 3.78 (1H, dq, J=9.5 and 7.1 Hz, OCH_2CH$_3$), 3.67 (3H, s, CO$_2$CH$_3$), 3.46 (1H, dq, J=9.5 and 7.1 Hz, OCH_2CH$_3$), 3.19 (1H, dd, J=13.2 and 2.7 Hz, CH_2Ph), 1.22 (3H, t, J=7.1 Hz, CH$_2$CH_3), and 0.85 (3H, s, 2-CH$_3$); ^{13}C NMR δ=174.54, 140.91, 129.33, 128.14, 125.73, 102.75, 81.33, 62.78, 51.67, 45.09, 42.85, 39.74, 34.76, 34.29, 33.63, 31.25, 28.89, 25.61, 25.20, 23.69, and 15.34.

14a (lower R_f): An oil; ^{1}H NMR δ=7.3—7.15 (5H, m, Ph), 5.20 (1H, dd, J=5.8 and 5.1 Hz, OCH(OEt)), 3.92 (1H, dq, J=9.5 and 7.1 Hz, OCH_2CH$_3$), 3.76 (1H, dd, J=10.5 and 6.1 Hz, 6-H), 3.67 (3H, s, CO$_2$CH$_3$), 3.52 (1H, dq, J=9.5 and 7.3 Hz, OCH_2CH$_3$), 3.22 (1H, dd, J=12.9 and 3.0 Hz, CH_2Ph), 1.29 (3H, t, J=7.1 Hz, CH$_2$CH_3), and 0.82 (3H, s, 2-CH$_3$).

Methyl (1*R*,2*R*,3*S*,5*S*,6*S*)-3-[3-Acetoxy-5-ispropenyl-2-methyl-8-oxo-7-oxabicyclo[4.3.0]non-2-yl]propionate (22). To a mixture of **13a** and **13′** (212 mg) in acetone (4 ml) cooled to 0 °C was added Jones reagent (1.2 ml) and the solution was stirred at room temperature for 40 min. Water was added and the product was extracted with chloroform five times. The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude oily product was chromatographed on silica gel (8 g). Elution with hexane–ethyl acetate (4 : 1) gave the lactone **22** (100 mg, 51%) and **22′** (10 mg, 5%).

22: An oil; IR 3080, 1780, 1735, 1650, 1440, 1380, 1245, 1170, 1043, 1010, 985, and 900 cm^{-1}; ^{1}H NMR δ=4.96 (1H, dd, J=11.2 and 4.4 Hz, 3-H), 4.92 (1H, d, J=1.5 Hz, =CH$_2$), 4.86 (1H, s, =CH$_2$), 4.57 (1H, dd, J=10.8 and 6.8 Hz, 6-H), 3.71 (3H, s, CO$_2$CH$_3$), 2.07 (3H, s, CH$_3$CO$_2$), 1.78 (3H, s, =CCH$_3$), and 0.94 (3H, s, 2-CH$_3$) (The assignment was performed by the ^{1}H–^{1}H COSY spectrum); ^{13}C NMR δ=174.93, 173.88, 170.35, 143.17, 113.32, 78.75, 74.53, 51.87, 45.86, 44.58, 37.48, 29.69, 29.12, 28.90, 27.91, 21.72, 21.07, and 20.44; MS m/z 338 (M$^+$, 11), 296(29), 278 (M$^+$$-CH_3CO_2$H, 49), 227(62), 210(94), 191(67), 149(49), 121(58), 107(65), and 97(100). Found: m/z 338.1780. Calcd for C$_{18}$H$_{26}$O$_6$: M, 338.1730.

22′: An oil; ^{1}H NMR δ=4.91 (1H, br s, =CH$_2$), 4.81 (1H, br s, =CH$_2$), 4.72 (1H, dd, J=11.2 and 3.7 Hz, 3-H), 4.57 (1H, dd, J=4.2 and 4.2 Hz, 6-H), 3.67 (3H, s, CO$_2$CH$_3$), 2.09 (3H, s, CH$_3$CO$_2$), 1.82 (3H, s, =CCH$_3$), and 1.04 (3H, s, 2-CH$_3$). Assignment of the peak at δ=4.72 was performed on the basis of the long-range spin coupling between 3-H and 2-CH$_3$. The stereochemistry was determined by the vicinal spin coupling constants of 3-H (axial) and 6-H (equatorial). This shows that **22′** was derived from the *cis*-allylic alcohol **18′**.

Methyl (1*R,2*R**,5*S**,6*S**)-3-[6-Benzyl-2-methyl-8-oxo-7-oxabicyclo[4.3.0]non-2-yl]propionate (23).** Compound **14a** (35 mg) was treated with Jones reagent (0.3 ml) as described above. After work-up the oily crude product was chromatographed on silica gel (20 g). Elution with hexane–ethyl acetate (10 : 1) gave the lactone **23** (23 mg, 65% yield), an oil; IR 3030, 1778, 1735, 1605, 1500, 1455, 1320, 1165, 1000, 890, 830, 750, and 700 cm^{-1}; ^{1}H NMR δ=7.23 (5H, m, Ph), 4.35 (1H, dd, J=10.0 and 5.6 Hz, 6-H), 3.69 (3H, s, CO$_2$CH$_3$), 3.18 (1H, dd, J=13.2 and 2.9 Hz, CH_2Ph), and 0.86 (3H, s, 2-CH$_3$); ^{13}C NMR δ=176.33, 173.94, 139.20, 129.30, 128.32, 126.17, 82.23, 51.77, 45.51, 41.90, 39.15, 34.35, 32.86, 30.32, 30.03, 28.45, 25.21, and 23.17; MS m/z 330 (M$^+$, 7), 299 (M$^+$$-CH_3$O, 3), 239 (M$^+$$-CH_2$Ph, 44), 151(85), 92(100), 91 (CH$_2$Ph, 100), 86(45), and 84(71). Found: m/z 239.1284. Calcd for C$_{13}$H$_{19}$O$_4$: M$-$CH$_2$Ph, 239.1283.

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