4-Oxatricyclo[5.2.1.0^{2,6}]decan-10-one and 4-Oxatricyclo[5.2.1.0^{2,6}]dec-8-en-10-one. Experimental and DFT Investigations of the π-Selectivities

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Received July 18, 2001

Abstract: Ab initio MO and experimental π-selectivities of hydride additions to 4-oxatricyclo[5.2.1.0^{2,6}]decan-10-one and 4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-10-one are described. The interactions of σ_{C1-C2} and σ_{C6-C7} with $\pi^*_{C=O}$, on one hand, and those of σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C=O}$, on the other hand, support *anti*-selectivities for both. This is in full accordance with the experiments. The arguments that are based on electrostatic interactions and electron donation from the ring oxygen do not apply.

Norbornan-7-ones have been the subject of intense experimental and theoretical investigations for their π-selectivities caused by the *endo*-substituents at positions 2 and 3.[1] Unlike cyclohexanones, norbornan-7-ones are considered rigid and devoid of significant geometrical distortion around the carbonyl function. The preference of 2,3-bis(methoxymethyl)norbornan-7-one (**1a**, Figure 1) for the *anti* addition of a nucleophile was attributed to through-space electron donations to σ_{C1-C2} and σ_{C3-C4} from the oxygen electron pairs in a rigid conformer such as **2** for the 2,3-divinyl species **1b**.[1,2] In **2**, the vinyl π-bonds are held parallel to σ_{C1-C2} and σ_{C3-C4}.[1a]

From the transition state structures for LiH additions to a series of 2,3-disubstituted-7-norbornanones, Houk and co-workers[3] have concluded that the hyperconjugation effects[4] were less important than the electrostatic effects for the control of diastereoselection. Electron-withdrawing substituents induced positive charges on C2/C3 and *syn* addition was favored. Likewise, electron-donating substituents induced negative charges on C2/C3 and *anti* addition was favored. This rationale, however, does not find qualified support as **1a** and **1b** favored *anti* addition and **1c** the *syn* addition. The substituents in **1a-c** are all electron withdrawing.

To evaluate the above arguments, we chose to study 4-oxatricyclo[5.2.1.0^{2,6}]decan-10-one, **3**, wherein the ring oxygen is held in such a rigid conformation (Figure 2) that it indeed raised the possibility of electron donation from one of its electron pair orbitals to σ_{C1-C2} and σ_{C6-C7} that, in turn, will favor *anti* selection. Alternatively, the electron-withdrawing ring oxygen will be expected to reduce the residual charges on C2 and C6 and promote *syn* selection in compliance with the electrostatic model. We have also studied 4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-10-one, **4**, to examine the competing effect of the unsaturation to that of the heterocyclic ring. The π-route[5] predicts, a priori, the *syn* selectivity. The electrostatic repulsion between the olefin and the nucleophile, both electron rich, also favors *syn* addition.[6] The *syn* addition requires the nucleophile to approach the carbonyl function from the side of the 5-ring heterocycle. The addition otherwise is *anti*. We report our results herein.

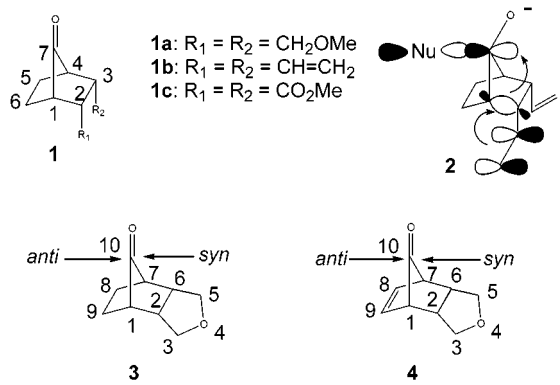

Figure 1. Structures of the species **1**−**4**.

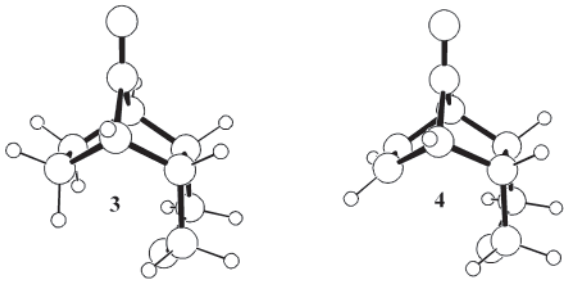

Figure 2. 3D structures of the species **3** and **4**.

Compounds **3** and **4** were prepared as shown in Scheme 1.[5] The Diels−Alder adduct **5**, obtained from the cycloaddition of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and maleic anhydride,[7] was reduced to **6**.[1a] Removal of the Cl atoms leading to **7** followed by catalytic reduction of the olefinic bond,[1a] closure of the heterocyclic ring,[8] and hydrolysis of the acetal function, in that order, furnished **3**. Likewise, closure of the heterocyclic ring in **7** and hydrolysis of the acetal function furnished **4**.

The selectivities of **3** and **4** with selected hydrides are collected in Table 1. There is a strong dependence of the selectivity on the specific hydride used and the reaction solvent employed. The selectivity has even reversed, as shown, with the use of L-Selectride for the reaction of **3**. Unlike most other reducing species that favored *anti*

† Fax: Int. Code-91-512-597436.

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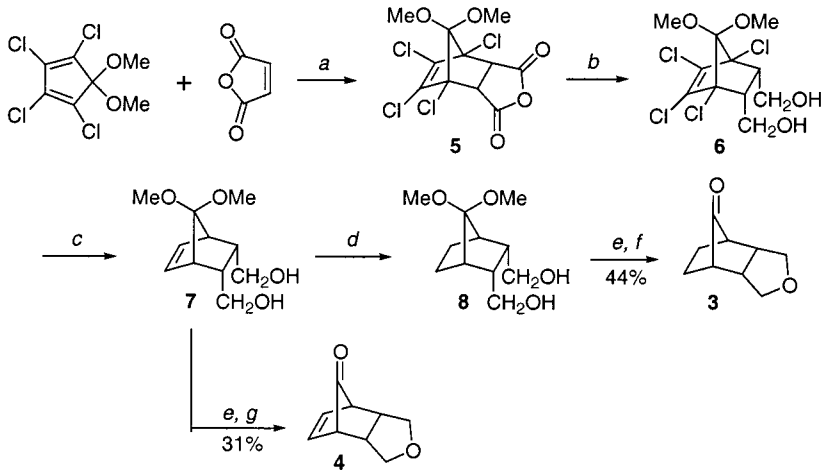
10.1021/jo015945t CCC: $22.00
Published on Web 12/27/2001

Scheme 1. Syntheses of Species 3 and 4



a. xylene, reflux, 3h, 90%; *b*. $LiAlH_4$, THF, reflux, 3h, 70%; *c*. Na, liq. NH_3, THF, 84%; *d*. Pd/C,H_2, EtOAc, 96%; *e*. TsCl, Py, 0 °C; *f*. 5% HCl in THF, 0-25 °C, 30 min; *g*. *p*-TSA, acetone, reflux, 8h

Table 1. π-Selectivities of Hydride Addition to 3 and 4

entry	**3**/**4**	hydride	solvent	Lewis acid	time (h)	yield (%)	*anti*:*syn*[a]
1	**3**	$NaBH_4$	MeOH		0.5	>95	1.0:1.0
2	**3**	$NaCNBH_3$	MeOH	pH 3−4	0.5	>95	2.1:1.0
3	**3**	$LiAlH_4$	Et_2O		2.0	>80	1.1:1.0
4	**3**	DIBAL-H	toluene		2.0	>85	2.0:1.0
5	**3**	DIBAL-H	toluene	$TiCl_4$ (3 equiv)	0.5	>85	4.8:1.0
6	**3**	L-Selectride	THF		1.0	>95	1.0:1.5
7	**3**	L-Selectride	toluene		1.0	>85	1.0:8.0
8	**3**	L-Selectride	toluene	$TiCl_4$ (3 equiv)	2.0	>80	1.3:1.0
9	**4**	$NaBH_4$	MeOH		1.0	>85	23:1.0
10	**4**	$NaCNBH_3$	MeOH	pH 3−4	1.0	>95	25:1.0
11	**4**	$LiAlH_4$	Et_2O		2.0	>95	4.5:1.0
12	**4**	DIBAL-H	toluene		2.0	>75	1.8:1.0
13	**4**	DIBAL-H	toluene	$TiCl_4$ (3 equiv)	0.5	>85	>20:1.0
14	**4**	L-Selectride	THF		1.0	>85	15:1.0
15	**4**	L-Selectride	toluene		1.0	>85	2.3:1.0

[a] The C2- and C6-protons appeared downfield in the alcohols formed from *anti*-addition compared to the protons in the alcohols formed from *syn*-addition. This is due to the anisotropic effect of the carbinol oxygen on the C2- and C6-protons in the former materials.[1a]

addition, L-Selectride favored *syn* addition. The effect of solvent on the reaction with L-Selectride is phenomenal; the selectivity changed from 1:1.5 in THF (entry 6) to 1:8 in toluene (entry 7).

The species **4** exhibited *anti* selectivity throughout. The magnitude of the selectivity was, once again, highly dependent on the source of the hydride and the solvent. Throughout, there was no reversal in the selectivity of **4**. This is in contrast with the results for **3** and this demonstrates the dominant role of the π-bond in **4** in guiding nucleophiles to the carbonyl function *syn* to it. Coordination of the π-bond to the nucleophile through a cation and, thus, delivery of the nucleophile to the carbonyl function *syn* to the π-bond is a distinct possibility. The saturation of the π-bond in the products formed from **4** generated the same species as those obtained from the reaction of **3**.

Lewis acids promoted *anti* addition to both **3** and **4**. The exclusive *anti* addition of DIBAL-H to **4** in the presence of $TiCl_4$ in toluene (entry 13) is, indeed, remarkable when compared to the 1.8:1 selectivity observed in its absence (entry 12).

C2/C6 and C8/C9 in **3** and **4** carry NBO charges of −0.29 and −0.47 and −0.28 and −0.22 au, respectively.[9,10] These charges predict, respectively, *syn* and anti *additions* to **3** and **4** in accordance with Houk's electrostatic model. Whereas the charge difference in **4** is too small to explain its high *anti* selectivity, the weak *anti* selectivity of **3** observed with the commonly used hydride reagents such as $Na(CN)BH_3$ and $LiAlH_4$ is clearly against the model. $LiAlH_4$ is often used as a standard nucleophile to probe π-selectivities.

Second-order perturbation theory analysis of Fock matrix in NBO basis[11] showed the absence of any electron donation from the ring oxygen to σ^*_{C1-C2} and σ^*_{C6-C7} in **3** and **4**. Clearly, an interpretation of the *anti* selectivities of **3** and **4** based on electron donation from the substituent oxygen to σ_{C1-C2} and σ_{C6-C7} is faulty. The prominent interactions relevant to the π-selectivities of **3** and **4** are

(9) All geometry optimizations and calculations of NBO charges were performed at the Becke3LYP/6-31G* level using the program Gaussian 94, Revision C.2. Frish, M. J.; Trucks, G. W.; Schlegel, H. B.; Jones, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresnan, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1995.

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Table 2. Interactions Relevant to the π-Selectivities of 3 and 4

3/4	$\sigma_{C1-C2}-\pi^*_{C=O}$	$\sigma_{C1-C9}-\pi^*_{C=O}$	$\sigma_{C6-C7}-\pi^*_{C=O}$	$\sigma_{C7-C8}-\pi^*_{C=O}$	$\sigma_{C3-H}-\sigma^*_{C1-C2}$	$\sigma_{C5-H}-\sigma^*_{C6-C7}$
3	3.32	3.19	3.32	3.19	2.94	2.94
4	3.51	2.76	3.51	2.76	2.83	2.83

listed in Table 2. The sum of the interactions of σ_{C1-C2} and σ_{C6-C7} with $\pi^*_{C=O}$ is superior to the sum of the interactions of σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C=O}$ in both the species.

Let us now understand why σ_{C1-C2}-$\pi^*_{C=O}$ and $\sigma_{C6-C7}-\pi^*_{C=O}$ interactions are superior to $\sigma_{C1-C9}-\pi^*_{C=O}$ and $\sigma_{C7-C8}-\pi^*_{C=O}$ interactions, respectively. A σ_{C-C} bond is understood to be less electron donating than a σ_{C-H} bond.[12] The σ_{C-C} bonds on C2 and C6 in **3** and **4** may be considered further less electron donating because they are depleted of their electron densities by the electron-attracting oxygen. However, the geometrical feature of the heterocyclic ring in **3** and **4** is such that it allows the interaction of an oxygen electron pair with (a) a substituent σ^*_{C-C} (1.91 kcal mol^{-1} in **3**; 2.15 kcal mol^{-1} in **4**) that raises the energy of the corresponding σ_{C-C} and improves its electron-donating ability and (b) a σ^*_{C-H} on C3/C5 (7.16 kcal mol^{-1} in **3**; 7.47 kcal mol^{-1} in **4**). The latter raises the energy level of the corresponding σ_{C-H} that is near antiperiplanar to σ_{C1-C2} and σ_{C6-C7} (H−C3/C5−C2/C6−C1/C7 = 150.1° in **3** and 146.9° in **4**). This allows for $\sigma_{C3-H}-\sigma^*_{C1-C2}$ and $\sigma_{C5-H}-\sigma^*_{C6-C7}$ interactions that are, respectively, 2.94 kcal mol^{-1} and 2.83 kcal mol^{-1} strong in **3** and **4**. These interactions are responsible in enhancing the overall electron-donating abilities of σ_{C1-C2} and σ_{C6-C7} to $\pi^*_{C=O}$ that, in turn, support the generally observed *anti*-selectivities.

The arguments that are based on electron donation from the oxygen directly to σ_{C1-C2} and σ_{C6-C7} and the electrostatic interactions between the nucleophile and the residual charges on C2/C3 and C5/C6 in norbornan-7-one skeleton have little to do with the selectivities of **3** and **4**. Further, the π-route argument and the argument of electrostatic repulsion between a π-bond and a nucleophile are invalid to **4**. The experimental selectivities of both **3** and **4** are rather controlled by the antiperiplanar effects that render σ_{C1-C2} and σ_{C6-C7} more electron-rich than σ_{C1-C9} and σ_{C7-C8} by electron donation from a C−H bond on C3 and C5.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-LA400 instrument in $CDCl_3$. The signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. The separations were carried out either by gravity column chromatography over silica gel (100−200 mesh) or radial chromatography using silica gel 60 PF_{254} (E. Merck) coated plates. Mixtures of EtOAc and hexanes were used for chromatographic separations. Organic extracts were dried over anhydrous Na_2SO_4 and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

Typical Procedure for Reduction with $NaBH_4$. $NaBH_4$ (0.2 mmol) was added to a solution of the substrate (0.2 mmol) in MeOH (2 mL) at 0 °C. After the reaction mixture was stirred for the specified time given in Table 1, MeOH was removed. Saturated aqueous NH_4Cl (2 mL) was added to the residue and the product(s) were extracted into EtOAc (2 × 5 mL). The combined EtOAc solution was dried and the EtOAc evaporated. The residue, thus left, was filtered through a small column of silica gel to furnish a mixture of the desired alcohols.

Typical Procedure for Reduction with $Na(CN)BH_3$. A small crystal of methyl orange was added to a solution of the substrate (0.2 mmol) in MeOH (2 mL) at 0 °C. The solution turned yellow. Drops of 2 N HCl/MeOH were added so that the solution turned red. Now, $Na(CN)BH_3$ (0.2 mmol) was added slowly. Whenever the color of the reaction mixture started to turn to yellow during the addition of $Na(CN)BH_3$, drops of 2 N HCl/MeOH were added immediately to restore the red color. When the reaction was complete, it was concentrated under reduced pressure. Saturated aqueous NH_4Cl (2 mL) was added to the residue and the product(s) were extracted into EtOAc (2 × 5 mL). The combined EtOAc extract was dried and the EtOAc evaporated. The residue, thus left, was filtered through a small column of silica gel to furnish a mixture of the desired alcohols.

Typical Procedure for Reduction with $LiAlH_4$. $LiAlH_4$ (0.2 mmol) was added to a stirred solution of the substrate (0.2 mmol) in anhydrous Et_2O (2 mL) at 0 °C. After the reaction mixture was stirred for the specified time given in Table 1 at the same temperature, enough EtOAc (2 mL) and water (2 drops) were added to destroy the excess $LiAlH_4$. Saturated aqueous NH_4Cl (2 mL) was added to the residue and the product(s) were extracted into EtOAc (2 × 5 mL). This was filtered and the organic solution dried. The evaporation of the solvents and filtration of the residue, thus obtained, through a short column of silica gel furnished a mixture of the desired alcohols.

Typical Procedure for Reduction with L-Selectride. A 1 M solution of L-Selectride in THF (0.3 mL, 0.3 mmol) was added to a magnetically stirred solution of the substrate (0.2 mmol) in the solvent (1.7 mL) of choice at 0 °C. The stirring was continued at this temperature until the reaction was complete. MeOH (0.2 mL), 1 N NaOH (0.2 mL), and 30% H_2O_2 (0.2 mL) were added and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. Extraction with EtOAc (2 × 5 mL) followed by washing with brine, drying, and evaporation furnished a residue which was filtered through a short column of silica gel to furnish a mixture of the desired alcohols.

Typical Procedure for Reduction with DIBAL-H. A 1 M solution of DIBAL-H in toluene (0.3. mL, 0.3 mmol) was added to a stirred solution of the substrate (0.2 mmol) in anhydrous toluene (1.7 mL) at 0 °C. The stirring at 0 °C was continued until the reaction was complete. The reaction was quenched with 5% aqueous HCl (2 mL) and extracted with EtOAc (2 × 5 mL). The combined extract was washed with water (1 × 3 mL) and brine (1 × 3 mL). The residue obtained after solvent removal was filtered through a short column of silica gel to furnish a mixture of the desired alcohols.

General Procedure for the Reduction in the Presence of $TiCl_4$. $TiCl_4$ (0.6 mmol) was added slowly to a solution of the substrate (0.2 mmol) in a solvent (1.7 mL) at 0 °C. This was stirred at 0 °C for 15 min and then the hydride reagent (0.3 mmol) was added. After the reaction was complete, it was quenched with 5% aqueous HCl (2 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine and dried. The crude material obtained from solvent evaporation was filtered through a silica gel column to furnish the desired alcohols.

Preparation of 5. A mixture of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (2.77 g, 10.5 mmol) and maleic anhydride (0.981 g, 10 mmol) in dry xylene (15 mL) was refluxed for 3 h under an N_2 atmosphere. The reaction mixture, when cooled to 25 °C and filtered, furnished the desired product in crystalline form, 3.62 g, 88%.

Preparation of 6. To a suspension of $LiAlH_4$ (0.95 g, 25 mmol) in dry THF (10 mL) at 0 °C was added a solution of **5** (2.75 g, 7.6 mmol) in THF (15 mL) slowly. The reaction mixture was allowed to warm to room temperature and refluxed for 10 h. The reaction mixture was cooled to 0 °C and quenched with

(12) The issue of the relative electron-donating ability of σ_{C-H} vs σ_{C-C} has been widely debated. However, a consensus appears to have emerged lately that favors stronger electron donating ability of σ_{C-H} over that of σ_{C-C}. Gung, B. W. *Tetrahedron* **1996**, *52*, 5263.

enough EtOAc and water to destroy the excess of $LiAlH_4$. This was filtered and dried. The evaporation of the solvent furnished the crude product that was filtered through a short silica gel column to obtain **6**, 1.87 g, 70%.

Preparation of 7. A solution of **6** (1.29 g, 3.7 mmol) in dry THF (20 mL) was added to liquid NH_3 (300 mL) in a 500 mL two-necked round-bottom flask fitted with a KOH guard tube and a rubber septum and cooled to − 80 °C. To this, small Na pieces were added until the permanent blue color appeared. The NH_3 was allowed to evaporate to leave behind a residue to which saturated aqueous NH_4Cl (40 mL) was added. This was extracted with EtOAc (3 × 15 mL) and the extract washed with brine and dried. The removal of solvent furnished a residue that was purified by silica gel column chromatography to obtain the desired product, 0.66 g, 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08−6.06 (2H, m), 4.25−4.05 (2H, bs), 3.60−3.56 (2H, dd, J = 11.1 and 3.5 Hz), 3.46 (2H, t, J = 10.5 Hz), 3.24 (3H, s), 3.12 (3H, s), 2.87−2.83 (2H, m), 2.73 (2H, broad d, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 118.2, 62.1, 51.7, 49.7, 48.6, 42.7. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.65; H, 8.47. Found: C, 61.48; H, 8.34.

Preparation of 4. *p*-TsCl (0.321 g, 1.68 mmol) was added in portions over 1 h to a solution of **7** (0.360 g, 1.68 mmol) in pyridine (4 mL) at 0 °C. The reaction mixture was warmed to room temperature and refluxed for 5 h. The mixture was poured into water (10 mL) and extracted with chloroform (4 × 5 mL). The combined extracts were washed with water (1 × 6 mL) and 5% aqueous HCl (2 × 6 mL). Drying and solvent removal furnished a residue, 0.235 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24−6.22 (2H, m), 3.66−3.61 (2H, m), 3.49−3.46 (2H, dd, J = 9.0 and 2.9 Hz), 3.22 (3H, s), 3.14 (3H, s), 3.04−3.01 (2H, m), 2.95−2.92 (2H, quintet, J = 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 122.2, 69.3, 51.9, 49.8, 48.0, 45.1. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22. Found: C, 67.20; H, 8.10.

A solution of the above crude material and two crystals of *p*-TSA in acetone (10 mL) was refluxed for 8 h. The solvent was removed and the residue chromatographed over silica gel to obtain **4**, 0.080 g, 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50−6.48 (2H, m), 3.83−3.79 (2H, m), 3.54 (2H, broad d, J = 9.2 Hz), 3.14−3.09 (2H, m), 3.04−2.97 (2H, m); ^{13}C (100 MHz, $CDCl_3$) δ 201.4, 131,0, 70.4, 50.3, 41.6. Anal. Calcd for $C_9H_{10}O_2$: C, 71.97; H, 6.72. Found: C, 72.02; H, 6.60.

Preparation of 8. To a solution of **7** (0.660 g, 3.08 mmol) in EtOAc (10 mL) was added 5% Pd/C (0.010 g)d. The flask was evacuated at a water aspirator and the vacuum released in a balloon filled with H_2. The resultant solution was stirred at 25 °C under an H_2 atmosphere for 12 h. It was filtered through a short pad of Celite and concentrated on a Rotovap. The residue was chromatographed over silica gel to furnish **8**, 0.640 g, 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65−4.15 (2H, bs), 4.03−3.94 (2H, m), 3.59 (2H, d, J = 11 Hz), 3.3.0 (3H, s), 3.25 (3H,s), 2.55−2.40 (2H, m), 2.12−2.04 (2H, m), 1.63−1.53 (2H, m), 1.37 (2H, d, J = 8.1 Hz). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.07; H, 9.33. Found: C, 60.90; H, 9.22.

Preparation of 3. To a solution of **8** (0.200 g, 0.926 mmol) in dry pyridine (2 mL) was added *p*-TsCl (0.177 g, 0.926 mmol) in portions over a period of 1 h at 0 °C. After stirring for 4 h at 25 °C, the reaction mixture was poured into water (10 mL) and extracted with chloroform (4 × 5 mL). The combined extracts were washed with water (1 × 7 mL), 5% aqueous HCl (1 × 7 mL), and brine (1 × 7 mL). The solvent was removed to obtain a residue, 0.152 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (2H, d, J = 9.8 Hz), 3.46−3.42 (2H, m), 3.29 (3H, s), 3.28 (3H, s), 2.76−2.71 (2H, m), 2.08−2.03 (2H, m), 1.58−1.56 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.5, 68.6, 50.5, 42.8, 41.4, 20.8. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.16. Found: C, 66.50; H, 9.02.

The above residue was dissolved in 5% HCl in THF (5 mL) and stirred for 30 min at 25 °C. The reaction mixture was diluted with Et_2O (20 mL) and washed with water (2 × 10 mL) and brine (1 × 10 mL). Drying and solvent removal furnished a residue that was chromatographed over silica gel to obtain **3**, 0.062 g, 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (1H, d, J = 10.2 Hz), 3.61−3.57 (1H, m), 2.77−2.69 (1H, m), 2.06−1.99 (1H, m), 1.90−1.86 (1H, m), 1.71−1.57 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 68.9, 42.4, 37.6, 171. Anal. Calcd for $C_9H_{12}O_2$: C, 71.01; H, 7.95. Found: C, 70.90; H, 7.82.

Acknowledgment. V.K.Y. thanks Department of Science and Technology, Government of India, for financial assistance to the purchase of a SiliconGraphics Origin200 computer. R.B. thanks University Grants Commission, Government of India, for a fellowship.

JO015945T