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Stereoselective Syntheses of Bridgehead Hydroxy Compounds via Reductive Cyclization Reactions Promoted by Samarium Diiodide

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STEREOSELECTIVE SYNTHESES OF BRIDGEHEAD HYDROXY COMPOUNDS VIA REDUCTIVE CYCLIZATION REACTIONS PROMOTED BY SAMARIUM DIIODIDE

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Abstract: Cycloalkanones appended with an α,β-unsaturated carbonyl side chain react with 2.25 equivalents of samarium diiodide to form bicyclic or tricyclic bridgehead hydroxy compounds stereoselectively in moderate yield.

Bridgehead hydroxy compounds are important not only to physical organic studies but also to natural products syntheses.[1] These compounds are normally made by condensation,[2] dissolving metal induced reductive cyclization[3] or free radical cyclization.[4] Although monocyclic hydroxy and bicyclic angular hydroxy compounds can be prepared from the intramolecular

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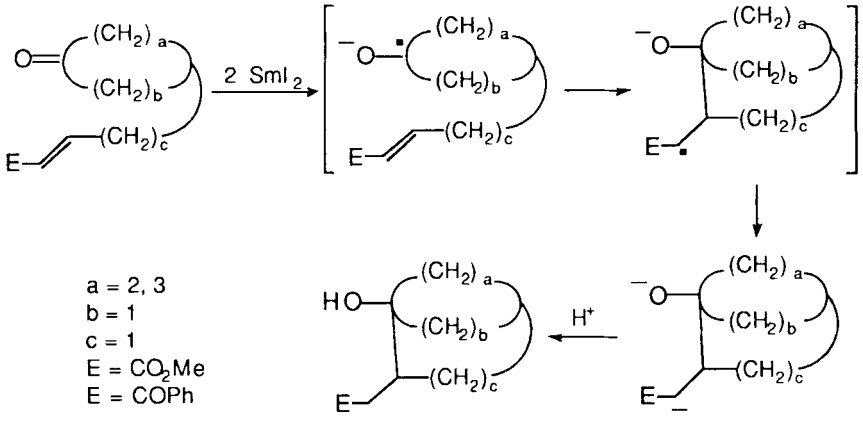


Scheme 1

addition reaction of an olefin containing ketyl which can be generated photochemically,[5] electrochemically,[6-8] and chemically,[9-12] bridgehead hydroxy compounds are rarely produced by these methods. The bridgehead carbocation, which can be generated from bridgehead hydroxy compound, is a useful intermediate for the carbon-carbon bond formation.[1,13] In the course of our studies directed towards the use of bridgehead carbocation in organic synthesis, we required a facile way to make bridgehead hydroxy compound. Conceptually, such a structural unit should be easily elaborated by an intramolecular addition of the ketyl to the β-center of the α,β-unsaturated carbonyl group as shown (scheme 1). In this report, we summarize the results of our work in this direction.

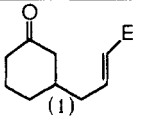
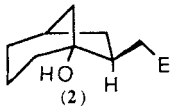
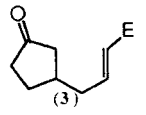
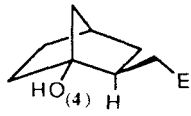
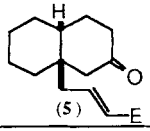
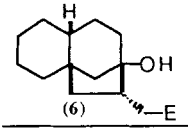
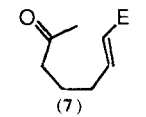
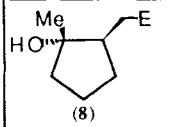
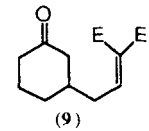
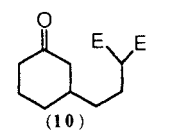
The cycloalkanones tethered to α,β-unsaturated esters or ketones were made from the corresponding enones by Sakurai reaction[14] followed by ozonolysis and Wittig reaction.[15] The standard procedure for the cyclization reactions is as follows: To the mixture of a keto-enoate (1.13 mmol), THF-HMPA (11 mL, 10 : 1) and *tert*-butyl alcohol (0.11 mL, 1.13 mmol) was added

a THF solution (blue) of SmI_2 (0.2M, 12.7 mL) at room temperature with stirring under nitrogen. The color of the solution turned to brownish readily. The reaction was complete within 20 minutes upon which time it was quenched with 1N HCl. After usual work-up, the crude material was purified by silica gel column chromatography to give the cyclized products in moderate yield. The signal corresponding to the the carbon bearing the bridgehead hydroxy group appeared at δ 78-79 in ^{13}C NMR is the diagonostic absorption for the cyclization product.[16] The results of the reductive cyclization reaction are summarized in Table 1.

It is noteworthy that α,β-unsaturated esters are more effective than α,β-unsaturated ketones in trapping the ketyl intermediates. Although the α,β-unsaturated ester, nitrile and phenyl group have been used as acceptors,[12] there is no successful examples where α,β-unsaturated ketones act as acceptors in reductive cyclization reactions. Products resulting from the straight reduction of the carbonyl or the double bond were not detected in our systems except in entry 5.[17] The result in entry 5 shows the better ability of an alkylidene malonate in accepting electrons than a ketone.

In each of the cyclization products shown in Table 1, the major isomer posseses a *trans* relationship between the hydroxyl and CH_2E group (E=CO_2Me, COPh) about the newly formed C-C bond. The assignment of the *trans* stereochemistry of these major products was based on the following reasons. First, lactone formation could not be achieved by treating compound (**2a**) with DBU in refluxing benzene for 24 hours. This indicates the correctness of the stereochemistry assignment since only the *endo* isomer is expected to cyclize due to the absence of the ring strain. Second, compound (**8a**) is known in literature[8] and its spectral data are identical with those

Table 1. The formation of bridgehead hydroxy compounds via reductive cyclization reaction induced by samarium diiodide

entry	starting material	product		yield[a]%	diastereo-selectivity
1	 (1)	 (2)	a. E=CO_2Me	70	> 99 : 1[c]
			b. E=COPh	60	> 99 : 1[c]
2	 (3)	 (4)	a. E=CO_2Me	80	> 99 : 1[c]
			b. E=COPh	57	> 99 : 1[c]
3	 (5)	 (6)	a. E=CO_2Me	76	24 : 1[b]
			b. E=COPh	63	14 : 1[b]
4	 (7)	 (8)	a. E=CO_2Me	74	> 99 : 1[c]
			b. E=COPh	50	> 99 : 1[c]
5	 (9)	 (10)	E= CO_2Me	45	—

[a] Satisfactory ^1H, ^{13}C NMR, IR, exact mass data and/or elementary analyses were obtained. [b] The ratio was determined by capillary GC on a HP-17 (10m x 0.53mm x 2.0 μm), CP-Sil 5CB (50m x 0.32mm x 0.27 μm) or Ultra 1 (25m x 0.2mm x 0.11μm). [c] The ^{13}C NMR spectrum indicates that only one isomer exists. The diastereoselectivities observe in all reactions shown in entries 1, 2, and 4 exceed the limits of capillary GC detection.

obtained in our laboratory.(entry 4a) Since one would expect that all the intramolecular addition reactions should follow similar pathways, the *trans* stereoselectivity in the reactions giving (**2a**) and (**8a**) should be also observed in all the other reactions. The electrostatic repulsion and the nonbonding interaction between the oxygen anion and CH_2E group[6,7,12] (E=CO_2Me, COPh) cause the CH_2E group to adopt the *exo* orientation in the bicycloalkane

intermediates during cyclization so that very high stereoselectivities were observed. It is interesting to point out that compound (**7**), under similar condition but at reflux temperature, gave a mixture of *trans*- and *cis*-isomers in a ratio of 9:1.[11] Presumably carrying out the reaction at lower temperature gives the cyclized compound with better stereoselectivity.

In conclusion, samarium diiodide can be utilized to induce the formation of bridgehead hydroxy compounds efficiently from the corresponding cycloalkanones appended with an α,β-unsaturated esters or ketones with excellent stereoselectivity.

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16. The spectroscopic data for the cyclized compounds in this work are: **Compound 2a** white solid (m.p.=48-49.5°C); ^{1}H NMR ($CDCl_3$) δ 1.00-2.24 (m, 12H), 2.52 (dq, J=16.3 and 5.4 Hz, 2H, CH_2-C=O), 2.91 (s, 1H, O-H), 3.69 (s, 3H, O-CH_3); ^{13}C NMR ($CDCl_3$) δ 19.06, 30.90, 32.91, 33.27, 34.85, 42.70, 46.76, 51.60 (O<u>C</u>H3), 77.88 (<u>C</u>-OH), 174.88 (C=O); IR (CH_2Cl_2) ν_{max} (cm^{-1}): 3414 (br, OH), 1734 (C=O); MS (m/z): 198

(M^+), 180, 167, 155 (base peak), 150; Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.60; H, 9.15. Found: C, 66.57; H, 9.44.

Compound 2b colorless oil; ^1H NMR ($CDCl_3$) δ 1.11-2.60 (m, 12H), 3.27 (d, J= 6.9 Hz, 2H, $CH_2C=O$), 3.60 (s, 1H, O-H), 7.43-7.58 (m, 3H, Ph-H), 7.97 -8.02 (m, 2H, Ph-H); ^{13}C NMR (CDCl3) δ 19.35, 31.08, 33.33, 35.36, 38.21, 42.37, 47.07, 77.94 (C-OH), 128.09, 128.50, 133.15, 136.90, 201.88 (C=O); IR (neat) ν_{max} (cm^{-1}): 3405 (-OH), 1677 (C=O); MS (m/z): 244 (M^+), 226, 213, 201, 183, 171, 146, 124, 105 (base peak), 97, 81, 69, 57; HRMS (m/z): 244.1456 (M^+, $C_{16}H_{20}O_2$, calcd 244.1412).

Compound 4a colorless oil; ^1H NMR ($CDCl_3$) δ 0.96-2.45 (m, 10H), 2.50 (dq, J= 15.0 and 6.9 Hz, 2H, $CH_2C=O$), 3.15 (br s, 1H, O-H), 3.69 (s, 3H, $O-CH_3$); ^{13}C NMR ($CDCl_3$) δ 28.59, 30.43, 33.67, 35.51, 37.82, 39.91, 45.47, 51.84 ($O-CH_3$), 83.62 (C-OH), 175.10 (C=O); IR (neat) ν_{max} (cm^{-1}): 3419 (O-H), 1738 (C=O); MS (m/z): 184 (M^+), 169, 168, 155, 152, 123, 110, 83.

Compound 4b colorless oil; ^1H NMR ($CDCl_3$) δ 1.00-2.50 (m, 10H), 3.23 (d, J=6.7 Hz, 2H), 3.71 (br s, 1H, O-H), 7.47-7.59 (m, 3H, Ph-H), 7.98-8.02 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$) δ 28.82, 30.40, 33.76, 38.26, 39.36, 40.65, 45.53, 63.08, 79.84 (C-OH), 128.14, 128.52, 131.18, 133.23, 201.56 (C=O); IR (neat) ν_{max} (cm^{-1}): 3406 (-OH), 1678 (C=O); MS (m/z): 230 (M^+), 212, 201, 184, 157, 146, 133, 125, 110, 105 (base peak), 95, 83, 71; HRMS (m/z): 230.1303 (M^+, $C_{15}H_{18}O_2$, calcd 230.1306).

Compound 6a colorless oil; ^1H NMR ($CDCl_3$) δ 1.26-1.90 (m, 17H), 2.21-2.38 (m, 1H), 2.50 (dq, J= 16.2 and 5.4 Hz, 2H, $CH_2C=O$), 2.94 (br, 1H, O-H), 3.68 (s, 3H, $O-CH_3$); ^{13}C NMR ($CDCl_3$) δ 23.57, 26.48, 26.71, 28.97, 31.77, 33.52, 38.90, 42.11, 45.08, 51.65, 79.12 (C-OH), 174.86 (C=O); IR (neat) ν_{max} (cm^{-1}): 3407 (O-H), 1736 (C=O); MS (m/z): 252

(M+), 220, 201, 181, 167, 151 (base peak), 135, 113, 95, 83, 71, 57; HRMS (m/z): 252.1720 (M+, $C_{15}H_{24}O_3$, calcd 252.1725).

Compound 6b colorless oil; ^1H NMR ($CDCl_3$) δ 1.17-2.04 (m, 16H), 2.40-2.60 (m, 2H), 3.24 (d, J=7.2 Hz, 2H), 3.50 (br, 1H, O-H), 7.43-7.58 (m, 3H, Ph-H), 7.97-8.01 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$) δ 24.46, 27.57, 29.88, 32.99, 39.55, 39.78, 42.49, 43.48, 43.90, 44.89, 46.07, 79.05 (C-OH), 128.97, 129.37, 134.02, 137.57, 202.49 (C=O); IR (neat) ν_{max} (cm^{-1}): 34.47 (O-H), 1675 (C=O); MS (m/z): 298(M+), 280, 255, 227, 193, 151, 120, 105; HRMS (m/z): 298.1925 (M+, $C_{20}H_{26}O_2$, calcd 298.1932).

Compound 8a colorless oil; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H, C-CH_3), 1.24 (m, 1H), 1.55-1.78 (br m, 4H), 1.90-2.10 (m, 1H), 2.21-2.50 (m, 1H), 2.40 (dq, J=11.5 and 7.7 Hz, 2H, CH_2C=O), 2.64 (br s, 1H, O-H), 3.69 (s, 3H, O-CH_3); ^{13}C NMR ($CDCl_3$) δ 20.38, 22.93, 30.24, 34.90, 41.00, 46.31, 51.65 (O-CH_3), 79.26 (C-OH), 174.55 (C=O); IR (neat) ν_{max} (cm^{-1}): 3476 (O-H), 1728 (C=O); MS (m/z): 171 (M+-1), 149, 129, 116 (base peak), 97, 83, 71.

Compound 8b colorless oil; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3H, C-CH_3), 1.30-2.02 (m, 6H), 2.38-2.54 (m, 1H), 3.10 (d, J=6.8 Hz, 2H, CH_2C=O), 3.43 (br s, 1H, O-H), 7.47-7.62 (m, 3H, Ph-H), 7.96-8.01 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$) δ 21.08, 23.59, 30.97, 39.87, 41.41, 46.13, 79.05 (C-OH), 128.07, 128.52, 133.46, 136.71, 201.32 (C=O); IR (neat) ν_{max} (cm^{-1}): 3467 (O-H), 1675 (C=O); MS (m/z): 218 (M+), 200, 185, 157, 146, 133, 120, 113, 105 (base peak), 93, 81, 71; HRMS (m/z): 218.1304 (M+, $C_{14}H_{18}O_2$, calcd 218.1306).

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