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(*R*)-2,3-Cyclohexylideneglyceraldehyde, a novel template for facile and simple entry into chiral hydroxy γ-lactones: synthesis of (−)-muricatacin

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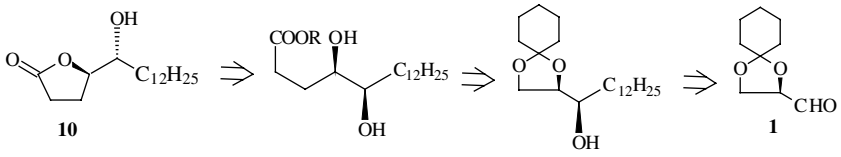
Abstract—(*R*)-2,3-Cyclohexylideneglyceraldehyde **1** has been used in a simple and efficient synthesis of (−)-muricatacin **10**. The required chiron, *syn*-alkanetriol **2a** was prepared by the reduction of a ketone **3** derived from **1**.

Muricatacin was isolated several years ago by McLaughlin and co-workers from the seeds of *Annona muricata* and was found to display cytotoxic activity against certain tumor cell lines.[1] The levorotatory natural material was shown to be a mixture of (4*R*,5*R*)-**10** and its enantiomer, with a slight predominance of the former. Muricatacin is a member of the hydroxy-lactone class of compounds that are notable for their biological activity and can be used as building blocks in the synthesis of complex bioactive natural products.[2] Furthermore, **10** is a good target to demonstrate the applicability of a synthetic methodology for the construction of functionalized γ-lactones. Several syntheses of either enantiomer of this chiral lactone **10** have been reported employing various strategies, viz the exploitation of chirons,[3] application of kinetic resolution,[4] stereo differentiating reactions,[5] etc. We present herein the preparation of **10** by a simple and efficient route starting from D-mannitol, which could also be applied for stereodivergent syntheses of various other functionalized γ-lactones.[6] Incidentally, reports are available on the use of D-mannitol for the synthesis of (−)-muricatacin.[3g,5e] However, as is evident from the following discussion our strategy is shorter, more straightforward and amenable to achieve greater stereochemical flexibility regarding the preparation of functionalized γ-lactones.

Retrosynthetic analysis of **10** (Scheme 1) suggested that an essential prerequisite was the generation of a functionalized (*R*,*R*)-1,2-diol. Earlier, we demonstrated that the (*R*,*R*)-1,2-diol moiety can be obtained from easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde **1**[7a] (Scheme 1) via oxidation of its alkylated products and *syn*-selective reduction of the resulting ketones with K-Selectride.[8] Compound **2a** was previously prepared from ketone **3** in high yield and with absolute stereoselectivity.[8b] For the present endeavor, reduction of **3** was carried out with $LiAlH_4$ and $NaBH_4$,[9] both of which afforded the desired products in good yields. From a



Scheme 1.

Keywords: (*R*)-2,3-Cyclohexylideneglyceraldehyde; $LiAlH_4$; *syn*-Selective reduction; Functionalized γ-lactones; Stereodivergent; (−)-Muricatacin.
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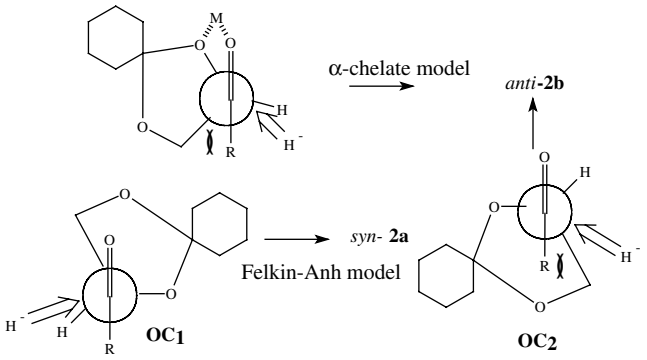
stereochemical viewpoint, while $NaBH_4$ reduction took place with poor selectivity (**2a**:**2b**, 55:45, overall yield 89%), reduction with $LiAlH_4$ resulted in good *syn*-selectivity (**2a**:**2b**, 85:15, overall yield 94%). High *syn*-selectivity has also been observed in the reduction of an α,β-unsaturated ketone obtained from **1**, with several hydrides.[10] The good *syn*-selectivity in the $LiAlH_4$ reduction of ketone **3** suggests that hydride addition takes place via a Felkin–Anh model[11] as in the case of K-Selectride reduction.[8] The somewhat lower *syn*-selectivity in this case suggests that there is a possibility of an α-chelation controlled reduction[12] in the presence of $LiAlH_4$. However, due to the presence of the bulky cyclohexylidene moiety in **3**, hydride attack takes place predominantly via the thermodynamically favorable conformation $\mathbf{OC_1}$ of the Felkin–Anh model rather than the $\mathbf{OC_2}$ or α-chelate model in order to avoid steric interactions (Scheme 2). However, the very poor selectivity during $NaBH_4$ reduction of **3** suggests an appreciable degree of α-chelate attack by the reagent.

Silylation of **2a** and deketalization of the resulting silyl ether **4** afforded diol **5** in high yield, which was converted to epoxide **7**[13] in two standard steps. Regioselective ring-opening of the epoxide **7** with allylmagnesium bromide produced **8**.[14] Following a known procedure[15] compound **8** was subjected to ozonolysis under basic conditions to afford the γ-lactone **9** directly, in good yield. This was then desilylated to produce the title compound **10** (Scheme 3) in 72% yield whose spectral and optical data were in conformity with those reported.[3a]

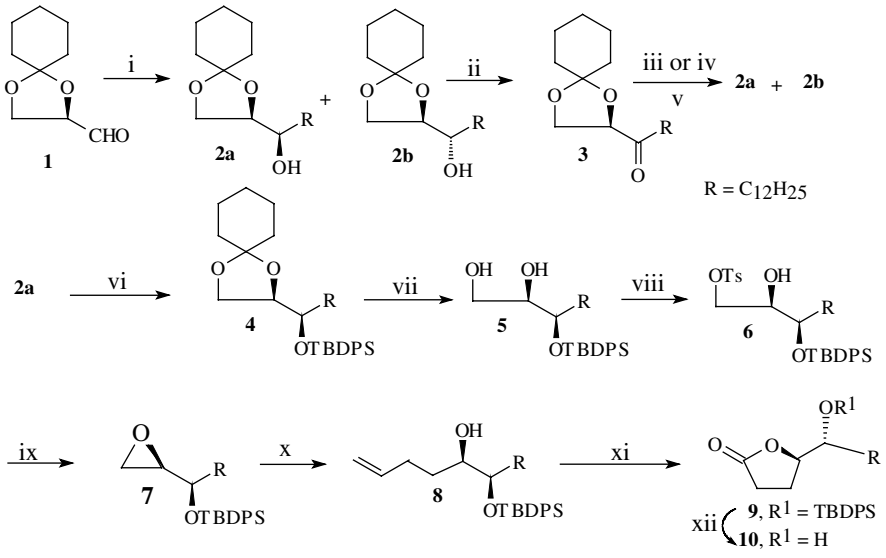
Thus a simple and efficient synthesis of **10**, a representative chiral hydroxy γ-lactone, has been developed starting from easily accessible **1**, itself derived from D-mannitol.[7a] The potential of $LiAlH_4$ and $NaBH_4$ for *syn*-selective reduction of ketone **3** was explored with $LiAlH_4$ proving to be better. Compared to the corresponding isopropylidene derivative,[16] the use of **1** is advantageous due to (i) the better stability of the cyclohexylidene ketal functionality and (ii) easy column chromatographic separation of the carbinol epimers **2a** and **2b**. Furthermore, the easy availability of various *anti*-alkane-1,2,3-triols[7] as the major products obtained from **1** and also of (*S*)-**1**[17] would extend the scope of the present protocol for the synthesis of different stereoisomers of the hydroxy γ-lactones with varied functional features.



Scheme 2.

References and notes

1. (a) Reiser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137–1140; (b) Cave, A.; Chaboche, C.; Figadere, B.; Harmange, J. C.; Laurens, A.; Peyrat, J. F.; Pichon, M.; Szlosek, M.; Cotte-Laffite, J.; Quero, A. M. *Eur. J. Med. Chem.* **1997**, *32*, 617–623.
2. (a) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217–7221; (b) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012–10020; (c) Avedissain, H.; Sinha, S. C.; Yazhak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035–6051; (d) Matsumoto, T.; Ichihara, A.; Ito, N. *Tetrahedron* **1969**, *25*, 5889–5892;



Scheme 3. Reagents and conditions: (i) RMgBr, 0 °C–rt, 76%; (ii) PCC, rt, 75%; (iii) $LiAlH_4$, THF, 0 °C, 94%; (iv) $NaBH_4$, MeOH, 0 °C, 89%; (v) column chromatography; (vi) TBDPSCl, Im, rt; (vii) CF_3CO_2H, H_2O, 0 °C, 88% (two steps); (viii) *p*-TosCl, Py, 0 °C; (ix) K_2CO_3, MeOH, rt, 85% (two steps); (x) allylMgBr, CuBr, −40 °C to rt, 78%; (xi) O_3, MeOH, NaOH, −15 °C, 75%; (xii) TBAF, THF, rt, 72%.

(e) Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.* **1974**, *96*, 7842–7844.
3. (a) Carda, M.; Rodriguez, S.; Gonzalez, F.; Castillo, E.; Villanueva, A.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, 2649–2655; (b) Figadere, B.; Harmange, J. C.; Laurens, A.; Cave, A. *Tetrahedron Lett.* **1991**, *32*, 7539–7542; (c) Pelletier, C. G.; Saniere, M.; Charvet, I.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron Lett.* **1994**, *35*, 115–118; (d) Saniere, M.; Charvet, I.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron* **1995**, *51*, 1653–1662; (e) Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 817–819; (f) Yoon, S. H.; Moon, H. S.; Hwang, S. K.; Choi, S. R.; Kang, S. K. *Bioorg. Med. Chem.* **1998**, *6*, 1043–1049; (g) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 2773–2775.
4. Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1993**, *34*, 1597–1598.
5. (a) Solladie, G.; Hanquet, G.; Izzo, I.; Crumbie, R. *Tetrahedron Lett.* **1999**, *40*, 3071–3074; (b) van Aar, M. P. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 11223–11234; (c) Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1994**, *59*, 4122–4125; (d) Wang, J. M.; Zhang, X. L.; Sharpless, K. B.; Sinha, S. C.; Sinha, A. B.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407–6410; (e) Rassu, G.; Pinna, L.; Spanu, P.; Zanardi, F.; Battistini, L.; Casiraghi, G. L. *J. Org. Chem.* **1997**, *62*, 4513–4517.
6. (a) Hanessian, S. *Total Synthesis of Natural Products : The Chiron approach*; Pergamon: Oxford, 1983; (b) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 4, pp 1–226; (c) Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298.
7. (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585–586; (b) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104–6107; (c) Chattopadhyay, A.; Dhotare, B.; Hassarajani, S. A. *J. Org. Chem.* **1999**, *64*, 6874–6878.
8. (a) Dhotare, B.; Chattopadhyay, A. *Synthesis* **2001**, 1337–1340; (b) Dhotare, B.; Salaskar, A.; Chattopadhyay, A. *Synthesis* **2003**, 2571–2575.
9. *$LiAlH_4$ reduction*: Hydride (0.02 mol) was added in portions over a period of 10 min to a THF solution of **3** (0.02 mol) at 0 °C and the mixture was stirred at 0 °C for 10 min. The excess hydride was decomposed by the addition of saturated aqueous Na_2SO_4. After filtration, the filtrate was concentrated by evaporation of the solvent under reduced pressure and column chromatography of the residue (silica gel, 0–20% EtOAc in hexane) afforded **2a** and **2b**. *$NaBH_4$ reduction*: Hydride (0.02 mol) was added to a MeOH solution of **3** (0.02 mol) at 0 °C over a period of 10 min and the mixture was stirred at 0 °C for 40 min. This was followed by usual work up and isolation of the products.
10. Murakami, T.; Furusawa, K. *Synthesis* **2004**, 1566–1572.
11. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205; (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–170.
12. Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.
13. Compound **7**: $[\alpha]_D^{25}$ −15.03 (*c* 6.5, $CHCl_3$); ^1H NMR: δ 0.87 (br t, 3H), 1.00–1.25 (m, 20H), 1.07 (s, 9H), 1.40–1.55 (m, 2H), 2.44 (dd, J = 5.0, 2.6 Hz, 1H), 2.70 (t, J = 5.0 Hz, 1H), 3.03 (m, 1H), 3.33 (m, 1H), 7.39 (m, 6H), 7.68 (m, 4H). Anal. Calcd for $C_{31}H_{48}O_2Si$: C, 77.44; H, 10.06. Found, C, 77.29; H, 10.24.
14. Compound **8**: $[\alpha]_D^{25}$ −11.9 (*c* 2.8, $CHCl_3$); IR: 3500, 3075, 3008, 2859, 1095, 910 cm^{-1}; ^1H NMR: δ 0.86 (br t, 3H), 1.00–1.24 (m, 22H), 1.06 (s, 9H), 1.50–1.80 (m, 2H, overlapped with s at 1.56 for 1H, OH), 1.90–2.20 (m, 2H), 3.40–3.60 (m, 2H), 5.00–5.20 (m, 2H), 5.70–5.90 (m, 1H), 7.40 (m, 6H), 7.65 (m, 4H). Anal. Calcd for $C_{34}H_{54}O_2Si$: C, 78.10; H, 10.41. Found, C, 78.22; H, 10.55.
15. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675–3680.
16. Jurczak, J.; Stanislaw, P.; Bauer, T. *Tetrahedron* **1986**, *42*, 447–488, and references cited therein.
17. Grauert, M.; Schollkopf, U. *Leibigs Ann. Chem.* **1985**, 1817–1824.