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(*R*)-2,3-Cyclohexylideneglyceraldehyde, a novel template for stereoselective preparation of functionalized δ-lactones: synthesis of mosquito oviposition pheromone

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Abstract—(*R*)-2,3-Cyclohexylideneglyceraldehyde **1** has been used to prepare functionalized δ-lactones. This was exemplified by a simple and efficient synthesis of the oviposition pheromone **10** of *Culex pipens fatigans*.

Chiral functionalized δ-lactones have drawn considerable attention in recent years due to their importance as building blocks in natural product synthesis.[1] In addition, the moiety is present in a large number of biologically important natural products.[1,2] 6(*S*)-Acetoxy-5(*R*)-hexadecanolide **10**, a functionalized δ-lactone, is the major component of the apical droplets that form on the eggs of the mosquito *Culex pipens fatigans*,[3] which is a possible vector of filarial diseases. The compound acts as an oviposition pheromone attracting gravid females of the same species and inducing them to oviposit in the same spot where the original eggs are found. The natural compound was shown to possess 5(*R*),6(*S*)-stereochemistry.[4] The synthesis of **10** in homochiral form assumes importance because of its utility from a social perspective. So far several syntheses of this chiral lactone **10** have been reported[5] where the required (*R,S*)-1,2-diol unit was obtained from suitable chiron sources[5g,k,m,n] or generated asymmetrically following different routes via microbial/metal hydride reduction[5d] of hydroxy ketones, Sharpless asymmetric epoxydation of allylic alcohols,[5a–c,i,j] Sharpless asymmetric dihydroxylations[5p] of an olefin, stereodifferentiating reactions,[5e,q] etc. Alternately, δ-lactone moiety of **10** was generated via a Ru catalyzed oxidative cyclization of a chiral 5-hydroxyacetylene.[5o] We report herein, a simple and efficient synthesis of **10** starting from (D)-mannitol by employing an asymmetric strategy which could also be applied for the synthesis of various other functionalized δ-lactones with varied stereochemistries.

We envisaged that the entire hydroxylactone moiety of **10** with its desired stereochemistry, could be obtained from the easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde **1**.[6a] Earlier, it had been observed that addition of *n*-decyl Grignard reagent to **1** took place with moderate *anti* selectivity, to produce (2*R*,3*S*)-**2b** as the major product (yield, 73%; **2a**:**2b**, 35:65).[6b] In the present work, **1** was treated with freshly prepared *n*-decyllithium in hexane or ether according to methods A and B.[7] In both the cases, the reagents (*n*-decyl bromide and lithium) were used in excess to ensure total consumption of the aldehyde. To our great delight, for both the cases the reactions took place with good yields and most importantly with very good *anti* selectivities, compared to that for the corresponding Grignard addition. (Method A: yield, 75%; **2a**:**2b**, 7:93; Method B: yield, 78%; **2a**:**2b**, 5:95). The *anti*-selectivity suggests that the alkyl attack in both Grignard and organolithium cases, takes place preferably via a Felkin–Anh model,[8] like hydride reductions of ketones derived from **1**.[6b–d] However, for both these organometallic additions there is some degree of possibility for α-chelate attack[9] under such anhydrous conditions. Probably, because of the presence of the bulky cyclohexylidene moiety in **1**, attack takes place predominantly via the thermodynamically favorable conformation $\mathbf{OC_1}$ of the Felkin–Anh model rather than

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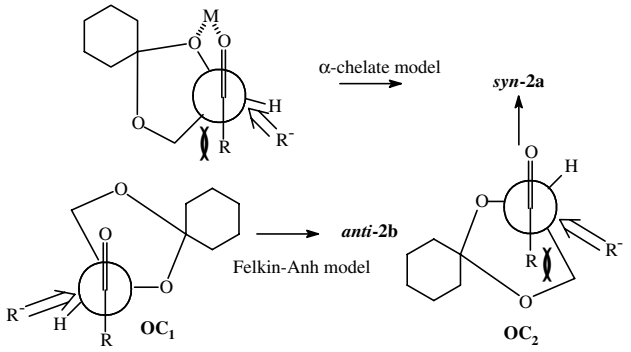


Scheme 1.

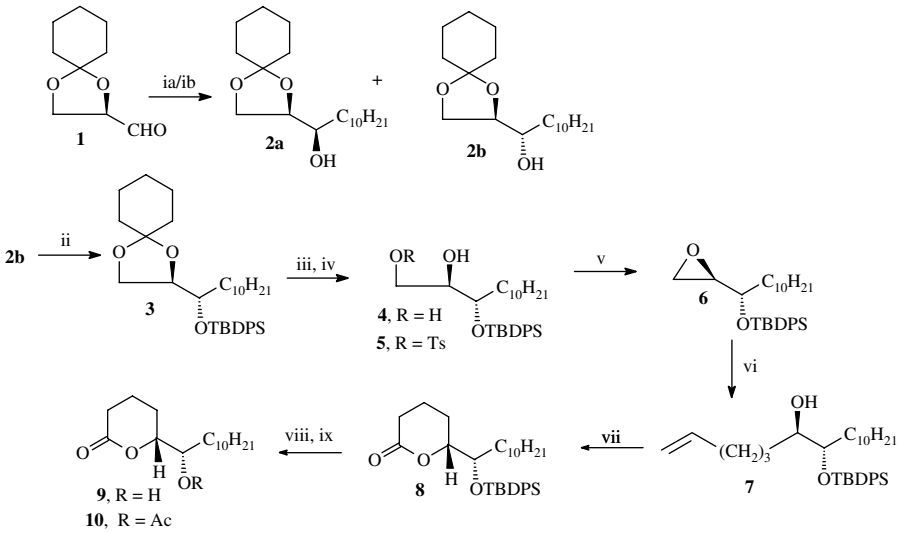
the **OC$_2$** or α-chelate model, in order to avoid steric interactions (Scheme 1). However, the production of a small amount of *syn*-**2a** during organolithium addition may reflect the smaller size of lithium, favoring chelate attack, with respect to the larger magnesium atom in the Grignard addition. This is supported by the fact that organocopper additions to the corresponding isopropylidene derivative of **1** were effected with high *syn* selectivity.[10]

Silylation of **2b** with TBDPS–Cl afforded **3**, which was deketalized in the presence of aqueous CF_3COOH (TFA) to obtain the diol **4** in good overall yield. Compound **4** was converted to the terminal epoxide **6**[11] via monotosylation of the primary hydroxyl group then base treatment of the resulting **5**. Regioselective ring opening of the epoxide of **6** with the Grignard reagent from 3-butenyl bromide produced **7**.[12] Following a known procedure,[13] **7** was subjected to ozonolysis under basic conditions to afford the δ-lactone **8** directly, in good yield, of which desilylation and subsequent acetylation produced the title compound **10**[14] in appreciable yield, the spectroscopic and optical data being in conformity with those reported[5j] for the natural product (Scheme 2).

Thus, a simple and efficient synthetic route to **10**, a representative chiral hydroxy δ-lactone has been developed starting from easily accessible **1**.[6a] Stereodifferentiating organolithium addition to **1** in hexane and ether was found to be highly *anti* selective. Earlier, conversions of **1** into *syn*-alkane-1,2,3-triols,[6b–d] several *anti* homoallylic,[15a,b] and homopropargyl alcohols[15a] with highly diastereoselectivity were described. The easy availability of these chiral carbinols and also of (*S*)-**1**[16] would extend the scope of the present protocol for the synthesis of different stereoisomers of the hydroxy δ-lactones with varied functional features.

References and notes

1. (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983; (b) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, pp 1–226; (c) Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298; (d) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4503–4504; (e) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725–2737; (f) Buisson, D.; Azerad, R. *Tetrahedron: Asymmetry* **1996**, *7*, 9–12; (g) Pearson, W. H.; Hemre, E. J. *J. Org. Chem.* **1996**, *61*, 7217–7221; (h) Warmerdam, E.; Tranoy, I.; Renoux, B.; Gesson, J. P. *Tetrahedron Lett.* **1998**, *39*, 8077–8080.
2. (a) Devon, T. K.; Scott, A. I. In *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1975; Vol. 1; (b) Friesen, R. W.; Vanderwal, C. *J. Org. Chem.* **1996**, *61*, 9103–9110; (c) Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833–5844.
3. Laurence, B. R.; Pickett, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 59–60.
4. Laurence, B. R.; Mori, K.; Otsuka, T.; Pickett, J. A.; Wadhams, L. J. *J. Chem. Ecol.* **1985**, *11*, 643–648.



Scheme 2. (ia) *n*-decyllithium, hexane, −40 °C to rt, 75%; (ib) *n*-decyllithium, ether, −40 to 0 °C, 78%; (ii) TBDPS–Cl, Im, rt; (iii) CF_3CO_2H, H_2O, 0 °C, 91% (two steps); (iv) *p*-TosCl, Py, 0 °C; (v) K_2CO_3, MeOH, rt, 89% (two steps); (vi) 3-butenyl-MgBr, CuBr, −40 °C to rt, 77%; (vii) O_3, MeOH, NaOH, −15 °C, 77%; (viii) TBAF, THF, rt, 69%; (ix) Ac_2O, Py, 0 to −10 °C, 79%.

5. (a) Mori, K.; Otsuka, T. *Tetrahedron* **1983**, *39*, 3267–3269; (b) Lin, G.; Xu, H.; Wu, B.; Guo, G.; Zhou, W. *Tetrahedron Lett.* **1985**, *26*, 1233–1236; (c) Barua, N.; Schmidt, R. *Tetrahedron* **1986**, *42*, 4471–4474; (d) Ramaswamy, S.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1145–1156; (e) Sato, T.; Watanabe, M.; Honda, N.; Fujisawa, T. *Chem. Lett.* **1984**, 1175–1176; (f) Ko, K. Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353–5362; (g) Masaki, Y.; Nagata, K.; Kaji, K. *Chem. Lett.* **1983**, 1835–1836; (h) Machiya, K.; Ichimoto, I.; Kirihata, M.; Ueda, H. *Agric. Biol. Chem.* **1985**, *49*, 643–649; (i) Wang, Z. M.; Qain, X. H.; Zhou, W. *Tetrahedron* **1990**, *46*, 1191–1198; (j) Bonini, C.; Checconi, M.; Righi, G.; Rossi, L. *Tetrahedron* **1995**, *51*, 4111–4116; (k) Kang, S. K.; Cho, I. H. *Tetrahedron Lett.* **1989**, *30*, 743–746; (l) Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981–5021; (m) Pelletier, C.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 1663–1674; (n) Gravier-Pelletier, C.; Saniere, M.; Charvet, I.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 115–118; (o) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528–2533; (p) Couladouros, E. A.; Mihou, A. P. *Tetrahedron Lett.* **1999**, *40*, 4861–4862, and references cited therein; (q) Courtrot, P.; Grison, C.; Bomont, C. *Tetrahedron Lett.* **1994**, *35*, 8381–8384.

6. (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585–587; (b) Dhotare, B.; Salaskar, A.; Chattopadhyay, A. *Synthesis* **2003**, 2571–2575; (c) Dhotare, B.; Chattopadhyay, A. *Tetrahedron Lett.* **2005**, *46*, 3103–3105; (d) Dhotare, B.; Chattopadhyay, A. *Synthesis* **2001**, 1337–1340.

7. Method A: *n*-Bromodecane (0.035 mol) in hexane (50 mL) was added over a period of 2 h to a stirred suspension of finely cut lithium (0.077 mol) in dry hexane (100 mL) at 10–15 °C under argon. The mixture was stirred at that temperature for 3 h more when the majority of lithium had dissolved. The suspension was cooled to −40 °C. To it a solution of **1** (0.01 mol) in THF (50 mL) was added over a period of 30 min. The mixture was stirred at −40 °C for 1 h, at 0 °C for 3 h and at room temperature overnight. It was then filtered quickly and the residue containing the unreacted lithium metal was washed with dry THF. [This excess lithium was later decomposed by treatment with cold MeOH.] The combined filtrates were treated with water and extracted with EtOAc. Solvent removal under reduced pressure and column chromatography of the residue (0–20% EtOAc in hexane) afforded **2a** and **2b**.Method B: *n*-Bromodecane (0.035 mol) in ether (50 mL) was added over a period of 3 h to a stirred suspension of finely cut lithium (0.077 mol) in dry ether (150 mL) at around −10 °C under argon. The mixture was stirred at −10 °C for 1 h further to dissolve the most of the lithium. The suspension was cooled to −40 °C. To it, a solution of **1** (0.01 mol) in ether (50 mL) was added over a period of 30 min. The mixture was stirred at −40 °C for 2 h, at −10 °C for 6 h, then filtered. After a normal work up, the products were isolated as in Method A.

8. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2205–2208; (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–170.

9. Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.

10. Sato, F.; Kabayashi, Y.; Takahashi, O.; Chiba, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1636–1638.

11. Compound **6**: $[\alpha]_D^{25}$ +7.8 (*c* 2.1, $CHCl_3$); IR (film): 3070, 3048, 2855 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (br t, 3H), 1.04 (s, 9H), 1.2–1.4 (m, 18H), 2.12 (dd, $J = 5.4$, 2.6 Hz, 1H), 2.45 (dd, $J = 5.06$, 3.92 Hz, 1H), 2.83–2.98 (m, 1H), 3.38 (dd, $J = 11.0$, 5.2 Hz, 1H), 7.39 (m, 6H), 7.64 (m, 4H).

12. Compound **7**: $[\alpha]_D^{25}$ +5.9 (*c* 2.8, $CHCl_3$); IR (film): 3500, 3075, 3005, 2857, 1095, 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (br t, 3H), 1.04 (s, 9H), 1.2–1.6 (m, 22H overlapped with s at 1.58 for 1H, OH), 1.9–2.05 (m, 2H), 3.4–3.6 (m, 2H), 5.0–5.2 (m, 2H), 5.7–5.9 (m, 1H), 7.36 (m, 6H), 7.65 (m, 4H).

13. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675–3680.

14. Compound **10**: $[\alpha]_D^{25}$ −36.5 (*c* 1.8, $CHCl_3$); Lit.[5j] $[\alpha]_D$ −36.7 (*c* 1.2, $CHCl_3$); IR (film): 1740, 1365, 1235, 1050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, $J = 7.2$ Hz, 3H), 1.22 (br m, 16H), 1.4–1.95 (m, 6H), 2.05 (s, 3H), 2.3–2.6 (m, 2H), 4.29–4.32 (m, 1H), 4.9–5.0 (m, 1H).

15. (a) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104–6107; (b) Chattopadhyay, A.; Dhotare, B.; Hassarajani, S. A. *J. Org. Chem.* **1999**, *64*, 6874–6878.

16. Grauert, M.; Schollkopf, U. *Leibigs Ann. Chem.* **1985**, 1817–1824.