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A Concise Synthesis of (-)-Dihydroprotolichesterinic Acid *via* Consecutive Stereocontrolled 1,4-Conjugate Addition and *syn*-Aldol Condensation Reactions

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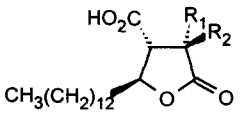
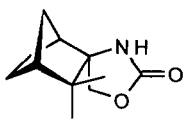
Abstract : (-)-Dihydroprotolichesterinic acid **1a** is synthesised in 6 steps and 57% overall yield by a strategy employing the camphene-derived chiral auxiliary **2** to construct the three contiguous stereogenic centres in consecutive stereocontrolled 1,4-conjugate addition and *syn*-aldol reactions.

Interest in the enantioselective synthesis of paraconic fatty acids has grown in recent years due to their biological significance. In particular, the tri-substituted γ-lactone (-)-dihydroprotolichesterinic acid [(3*S*, 4*R*, 5*S*)-4-carboxy-3-methyl-5-tridecyl-oxolan-2-one] **1a** is noted to be a potent antibacterial agent,[1] while (-)-protolichesterinic acid **1b**, recently synthesised enantiospecifically by Greene,[2] is known to possess anti-bacterial, anti-fungal, anti-tumoral and growth regulating properties.[3] The first enantiospecific synthesis of **1a** was carried out recently by Mulzer[4] in 14 steps from (3*R*)-2,3-isopropylidiene glyceraldehyde with an overall yield of 0.4%, while its enantiomer was obtained by a similar route in 0.5% from di-isopropylidiene-*D*-glucose.



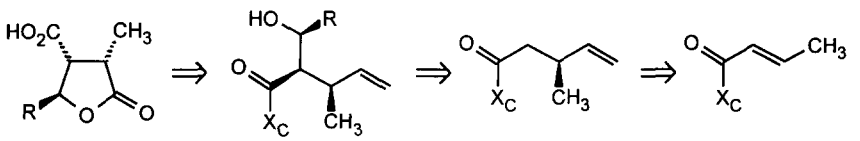
1a, $R_1 = CH_3$, $R_2 = H$

1b, $R_1, R_2 = =CH_2$



2

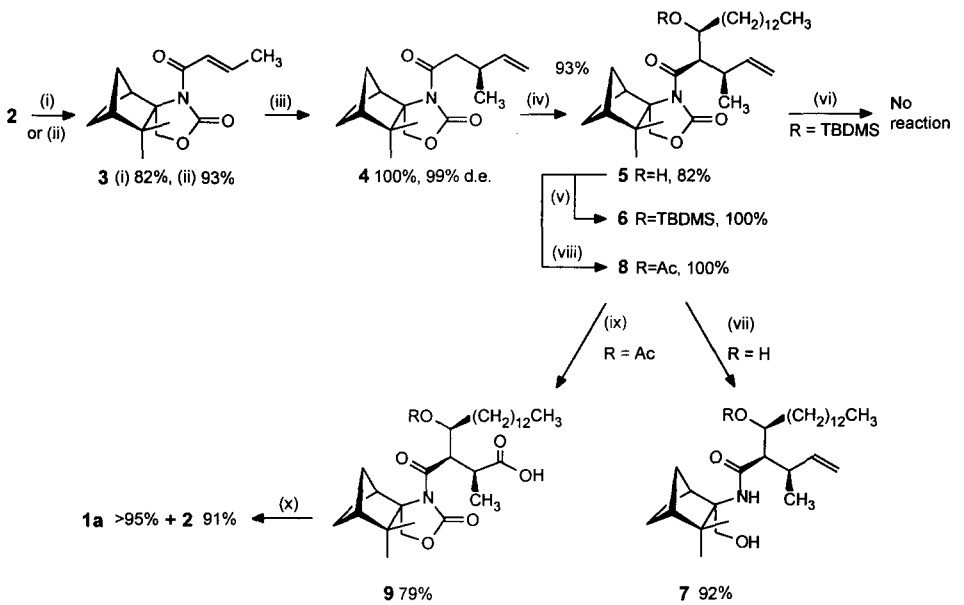
Herein we describe a much more consise and efficient synthesis of **1a** in which our recently developed camphene-derived chiral auxiliary **2** [(-)-Chiracamphox][5] is used to construct the three contiguous chiral centres *via* the successful strategy of consecutive stereocontrolled 1,4-conjugate addition and *syn*-aldol condensation reactions. In retrosynthetic analysis (Scheme 1) we masked the lactone carboxyl function as a vinyl group.



HX_C = **2**

Scheme 1

The synthesis begins with the crotonyl imide **3** which is conveniently prepared either by reaction of the bromomagnesium salt[6] of **2** with crotonyl chloride in 82% yield, or in 93% yield *via* the ethylzinc salt, a procedure developed by us[5c] to avoid *C*-acylation in the synthesis of acyl imides (Scheme 2).

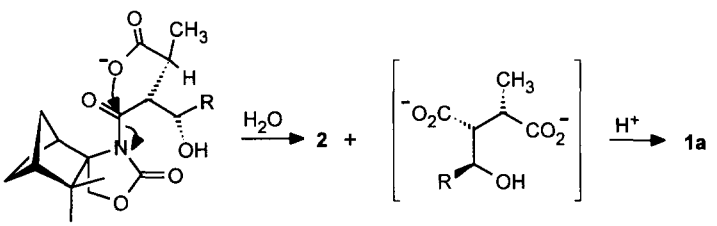


Scheme 2.

Reaction conditions: (i) EtMgBr, THF, 0°C, then *E*-crotonyl chloride, -78°C to rt. (ii) $ZnEt_2$, Et_2O, rt, then *E*-crotonyl chloride -78°C to 35°C, 3 hr. (iii) CH_2=CHMgBr (2.5 equiv.), CuBr (0.4 equiv.), -78°C to -20°C, then addition to sat. NH_4Cl/THF 0°C. (iv) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, -78°C to 0°C, then $CH_3(CH_2)_{12}CHO$, -78°C to rt. (v) TBDMSTOf, THF, -78°C to rt. (vi) $PhCH_2OLi$, THF, -78°C to rt, 5 days. (vii) . LiOH, H_2O_2, THF/H_2O, 50°C, 3 hr. (viii) Ac_2O, NEt_3, DMAP, hexane. (ix) $KMnO_4$, *n*-BuN_4Br, C_6H_6/AcOH/H_2O, 50°C, 1/2 hr. (x) LiOH, H_2O_2 (30%, 100 equiv.), THF/H_2O, rt, 5 days.

1,4-Conjugate addition of vinylmagnesium bromide to **3** under copper catalysis led to the quantitative formation of adduct **4** with near complete stereoselection. The absolute configuration of the new stereocentre in **4** was determined after catalytic reduction (H_2, 10% Pd/C, ethyl acetate, 1 atm.) of **4**, followed by cleavage with lithium hydroperoxide[7] to give (3*R*)-3-methylpentanoic acid $[\alpha]_D^{18}$= +4.5° (c = 2.0, $CHCl_3$), *lit.*[8] $[\alpha]_D^{23}$= +6.42° (c = 4.03, $CHCl_3$).

In the second stereocontrolled step, the dibutylboron enolate of **4** produced under standard conditions[9] was treated with tetradecanal to give the *syn*-aldol product **5** (CHOH.CHCO, J = 6.4 Hz) in 82% yield as a single diastereomer. Initially **5** was converted into its TBDMS ether **6**, but this failed to cleave when treated with lithium benzyloxide,[10] presumably due to shielding of the imide carbonyl by the long alkyl chain/TBDMS group. It was found that use of the smaller TMS ether grouping led to deprotection and subsequent decomposition of the aldol product due to the prolonged reaction time required. An attempt was made to cleave the unprotected aldol product **5**, but this failed to react with lithium hydroperoxide under mild conditions and gave only the β-amido alcohol **7**, formed by *endo*-cyclic attack in 92% yield when heated to 50°C. Not discouraged, we next investigated the possibility of assisted solvolysis of the desired fragment from the auxiliary. To this end, **5** was protected as its acetate **8** which was then oxidatively cleaved with potassium permanganate under modified phase-transfer conditions of Starks[11] to give the acid **9** in 79% yield. Treatment of **9** with lithium hydroperoxide (5 equiv.) under adapted conditions (see Scheme 2) led to the slow but complete removal of the chiral fragment in the required manner, and to our pleasure, the desired lactone **1a**. In this step it is believed that the neighbouring carboxylate (or percarboxylate) anion may be assisting in the cleavage of the imide bond by its attack on the *exo*-carbonyl (Scheme 3).



Scheme 3.

The crystalline lactone **1a** was isolated in >95% yield [m.p. = 105.1-105.8°C (from hexane/cyclohexane), *lit.*[12] m.p. = 106°C, $[\alpha]_D$= -53.0°(c = 1.75, $CHCl_3$), *lit.*[4] $[\alpha]_D$= -49.5° (c = 1.75, $CHCl_3$) and consistent spectroscopic data] whilst **2** was recovered in 91% yield with complete stereochemical integrity.

Thus an overall yield of 57% of chirally pure **1a** in six steps has been achieved, considerably shorter and higher yielding than the previous synthesis.[4] Our route represents a viable and easily adapted method for the formation of 4-carboxy-γ-lactones containing three contiguous chiral centres. We are at present attempting to apply this methodology to other similar systems as well as demonstrating the utility of **2** and its enantiomer in the synthesis of other small- and medium-sized chirally pure fragments.

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References

1. Cavallito, C. J.; McKencia Fruehauf, D.; Bailey, J. H., *J. Am. Chem. Soc.*, **1948,** *70,* 3724.
2. (a) Shibata, S.; Miura, Y.; Sugimura, H.; Toyoizumi, Y., *J. Pharm. Soc. Jpn.*, **1948,** *68*, 300; *Chem. Abstr.*, **1951,** *45*, 6691i. (b) Fujikawa, F.; Hitosa, Y.; Yamaoka, M.; Fujiwara, Y.; Nakazawa, S.; Omatsu, T.; Toyoda, T., *ibid*, **1953,** *73,* 135; *Chem. Abstr.*, **1954,** *48*, 230a. (c) Borkowski, B.; Wozniak, W.; Gertig, H.; Werakso, B., *Diss. Pharm.*, **1964,** *16*, 189; *Chem. Abstr.*, **1965,** *73*, 1995b. (d) Sticher, O., *Pharm. Acta Helv.*, **1965,** *40,* 385; ; *Chem. Abstr.*, **1965,** *63*, 12026c. (e) Hirayama, T.; Fujikawa, F.; Kasahara, T.; Otsuka, M.; Nishida, N.; Mizuno, D., *Yakugaku Zasshi,* **1980,** *100*, 755; ; *Chem. Abstr.*, **1980,** *100*, 179563f. (f) Huneck, S.; Schreiber, K., *Phytochemistry,* **1972,** 2429.
3. Murta, M. M.; de Azevedo, M. B. M.; Greene, A. E., *J. Org. Chem.*, **1993,** *58,* 7537.
4. Mulzer, J.; Salimi, N.; Hartl, H., *Tetrahedron Asymmetry,* **1993,** *4,* 457.
5. (a) Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Grant, K. J.; Hodgson, P. K. G.; and Thorburn, P., *Heterocycles,* **1994,** *37,* 199. (b) Banks, M. R.; Blake, A. J.; Brown, A. R.; Cadogan, J. I. G.; Gaur, S.; Gosney, I.; Hodgson, P. K. G.; and Thorburn, P., *Tetrahedron Lett.*, **1994,** *35,* 489. (c) Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Hodgson, P. K. G.; and Thorburn, P, *Acros Chimica Acta, in press* (1995), [**2**, Chiracamphox, is commercially available from Acros Chimica N.V. Janssen Pharmaceuticalaan 3,2440, Geel, Belgium, Cat. No. 29.643.58].
6. Evans, D. A.; Chapman, K. T.; Bisaha, J., *J. Am. Chem. Soc.*, **1988,** *110,* 1238.
7. Evans, D. A.; Britton, T. C.; Ellman, J. A., *Tetrahedron Lett.*, **1987,** *28,* 6141.
8. Kenji, M.; Shigefumi, K.; Hiraki, U.,*Tetrahedron,* **1983,** *39,* 2439.
9. Evans, D. A.; Bartroli, J.; Shih, T. L., *J. Am. Chem. Soc.*, **1981,** *103,* 2127.
10. Evans, D. A.; Ennis, M. D.; Mathre, D. J., *J. Am. Chem. Soc.*, **1982,** *104,* 1737.
11. Starks, C. M., *J. Am. Chem. Soc.*, **1971,** *93,* 195.
12. Asahima, Y.; Yanagita, M., *Ber. Dt. Chem., Ges.*, **1936,** *69,* 120.

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