AN EFFICIENT TOTAL SYNTHESIS OF (-)-MINTLACTONE AND (+)-ISOMINTLACTONE

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Abstract: Total synthesis of (-)-mintlactone and (+)-isomintlactone has been achieved diastereoselectively via a fused butenolide construction strategy based on an intramolecular [3+2] cycloaddition reaction of nitrile oxide.

The presence of the fused butenolide nucleus in a number of natural products of biological interest has spurred the development of synthetic strategies for preparing this ring system.¹ In connection with a continuing interest in developing the methodology for the construction of fused heterocycles, which would be useful in natural product synthesis,² based on the intramolecular [3+2] dipolar cycloaddition reaction,³ we were intrigued by the possibility of effecting conversion⁴ of an isoxazoline 1 into a fused butenolide 4 via a chemo- and diastereoselective metal hydride reduction of β -hydroxy keto ester 2 followed by lactonization and dehydration of 3. (Scheme 1)



In this communication, we report a total synthesis of (-)-mintlactone **5**, having a characteristic sweet aroma, and (+)-isomintlactone **6**, isolated from some *Mentha* species as minor components,⁵ employing the general strategy shown in Scheme 1. Although the conversion of (+)-menthofuran into (-)-**5**^{5b,6} and the syntheses of **5** and **6** as racemic modifications^{1,7} have already been accomplished, the highly enantio(diastereo)selective and efficient total syntheses of these monoterpenes are few.^{7c}

The olefinic acetal 7,⁸ derived from (+)-citronellal { $[\alpha]_D+14.3^\circ$, lit.⁹, $[\alpha]_D+17.4^\circ$ }, was ozonized and the resulting aldehyde was condensed with ethyl 2-(triphenylphosphoranylidene) propionate to provide an unsaturated ester 8. Acidic hydrolysis of the acetal 8 and subsequent oxime formation provided 9 in 57 % overall yield from 7. Treatment of 9 with 7 % aqueous sodium hypochlorite in dichloromethane at room temperature afforded a chromatographically

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separable diastereoisomeric mixture of isoxazolines, 10 and 11, in a ratio of 20 : 1 in 84 % yield. The stereostructure of the cycloadducts was tentatively assigned as shown from the mechanistic viewpoint.¹⁰ Reductive hydrolysis of the major adduct 10 with trimethyl borate in aqueous methanol in the presence of a catalytic amount of Raney nickel under a hydrogen atmosphere provided 12 in 81 % yield. With the β -hydroxy- β -carbethoxy ketone 12 in hand, we began to explore the diastereoselective hydride reduction of the carbony group and subsequent assembly of fused butenolide, the cornerstone of our synthetic strategy. Initial experiments for the conversion into 5 focused on the Evans¹¹ intramolecular hydride delivery of β -hydroxy ketone. Treatment of 12 with tetramethylammonium triacetoxyborohydride in acetonitrile-acetic acid at -40 °C - room temperature for 6.5 h afforded the corresponding 1.3-diol which was immediately treated with a catalytic amount of p-toluenesulfonic acid in methylene chloride to provide the lactones, 14 and 1512, in 88 % yield as an easily separable mixture of diastereoisomers in a ratio of 30:1. The configuration of the newly formed stereogenic center of the both isomers was deduced from a splitting pattern of the C-7a hydrogen in the ¹H-NMR spectrum and confirmed by the eventual conversion of the both into 5 and 6, respectively. Thus, dehydration of 14 with phosphorus oxychloride in pyridine produced 92 % yield of (-)-mintlactone 5, which was identical by 400MHz ¹H-NMR, capillary GC/MS, and optical rotation {[α]_D-50.3 °, lit.^{5d}, [α]_D-51.8 *) with the natural 5. Analogously, the minor isomer 15 was converted into (+)-isomintlactone 6 in 93 % yield, identical with an authentic sample by 400MHz ¹H-NMR, melting points (m.p. 81-82 °C, lit. m.p. 77-79 °C), optical rotation { $[\alpha]_D$ +76.8 °, lit.^{5d}, $[\alpha]_D$ +76.9 ° }, and capillary GC mass spectrometric comparisons. For the diastereoselective synthesis of 6, we examined several reducing agents and found zinc borohydride¹³ to be the best. Thus, treatment of **12** with zinc borohydride in ether at 0 °C for 5 min followed by acidic treatment gave the diastereoisomeric lactones, 15 and 14, in a ratio of 6 : 1 in 47 % yield. The stereochemical outcome was rationalized by considering a predominant attack of hydride from the re-face of carbonyl via the zinc-mediated transition state,^{13b} whose intervention was supported by the fact that the same treatment of the silvl ether 13 followed by desilvlation resulted in the formation of a mixture of 14 and 15 in a ratio of 5 : 1^{14} in 60 % vield. (Scheme 2)

The efficient and diastereoselective total synthesis of (-)-mintlactone and (+)isomintlactone described herein attests to the utility of a method for the construction of fused butenolides based on an intramolecular [3+2] dipolar cycloaddition reaction of nitrile oxide. Further application and generalization of this methodology are currently in progress in our laboratory.

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Reagents: a, O₃, Me₂S; b, Ph₃P=C(Me)CO₂Et, 70 %; c, 5% HCl; d, NH₂OH•HCl, AcONa, 82 %; e, 7% NaOCl, 84 %; f, H₂, Raney Ni, B(OMe)₃, 81 %; g, ¹BuMe₂SiOTf, 2,6-lutidine, 94 %; h, Me₄NBH(OAc)₃; i, *p*-TsOH, 88 %; j, Zn(BH₄)₂ then i, 47 %; k, POCl₃, pyridine, 92 % for 5, 93 % for 6.

Scheme 2

References and Notes

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- All new compounds were characterized by 200(or 400) MHz ¹H-NMR, IR and mass spectrometric and/or elemental analyses. Selected spectral and physical data for 14: Colorless prisms; m.p. 159-161 °C (Et₂O-hexane); [α]_D+57.2 ° (c=1.03, EtOH); IR (KBr) cm⁻¹: 3459 (OH) and 1753 (C=O); ¹H-NMR (200 MHz, CDCl₃) δ: 1.02 (3H, d, J=6.6 Hz, C-6 Me), 1.44 (3H, s, C-3 Me), 4.23 (1H, ddd, J=11.8, 9.9, and 3.9 Hz). For 15: Colorless prisms; m.p. 128-130 °C (Et₂O-hexane); [α]_D-35.2 ° (c=0.99, EtOH); IR (KBr) cm⁻¹: 3387 (OH) and 1758 (C=O); ¹H-NMR (200 MHz, CDCl₃) δ: 0.92 (3H, d, J=6.4 Hz, C-6 Me), 1.50 (3H, s, C-3 Me), 4.58 (1H, dd, J=6.3 and 2.9 Hz).
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- 14. Reduction of **12** with NaBH₄ followed by acidic treatment gave a mixture of **14** and **15** in a ratio of 3 : 1 in 48 % yield. Experimental details will be reported as a full article in due course.

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