

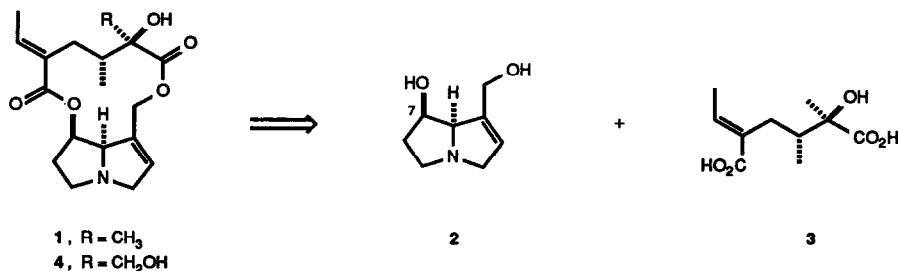
A NOVEL SYNTHESIS OF (+)-INTEGERRINECIC ACID LACTONE FROM R-(+)- β -CITRONELLOL

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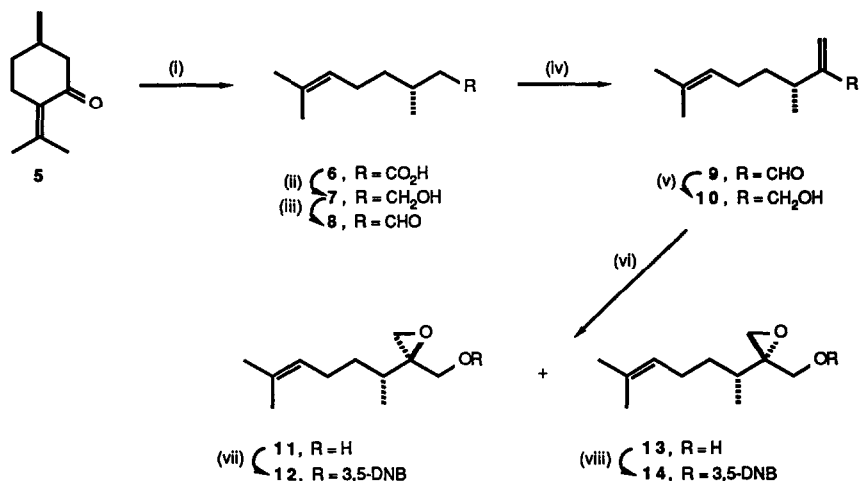
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SUMMARY: A new route to (+)-integerrinecic acid, the necic acid component of the macrolactone pyrrolizidine alkaloid integerrimine, has been devised starting from the R enantiomer of β -citronellol and proceeding via δ -lactone, 17.

Syntheses of integerrimine (1) have utilized a common strategy that assembles the dilactone moiety of this alkaloid from the natural diol (+)-retronecine (2) and a derivative, eg 19, of a dicarboxylic (integerrinecic) acid (3).¹⁻³ In the course of our synthesis of 1,³ (+)-lactone (19), prepared in 16 steps and 11% overall yield from methyl (R)-(-)-3-hydroxy-2-methylpropionate, was converted to 22 prior to regioselective coupling to the 7-hydroxyl function of 9-t-butyltrimethylsilyloxyretronecine. Although this route to the necic acid component of 1 afforded material of very high stereochemical purity, the need for HPLC separation at an early stage in the sequence presented serious logistical problems. Also, this approach could not be readily modified to accommodate other pyrrolizidine alkaloids, such as usaramine (4).



A more flexible plan for synthesis of 20 and, prospectively, those necic acids that bear a 3R methyl substituent can be envisioned from (R)-(+)- β -citronellol (7). Controlled introduction of the second stereogenic center and adjustment of functionality, including truncation at the isopropylidene terminus, are required to reach 15 and hence 22 from 7. We now describe a sequence that accomplishes this goal.

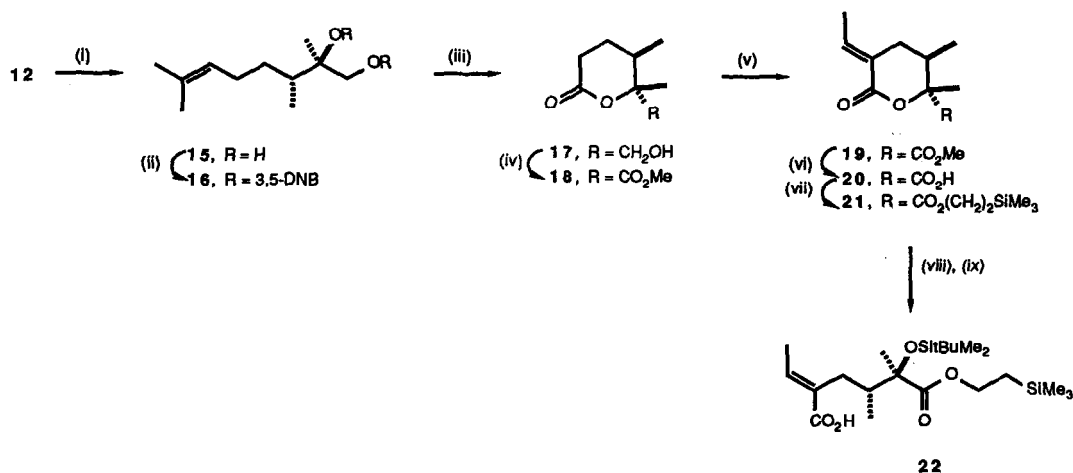


(i) HCl (g), -5 °C; NaOH, rt (53%); (ii) LiAlH₄, Et₂O (97%); (iii) Pyridinium chlorochromate, CH₂Cl₂ (70%); (iv) CH₂=NMe₂⁺ I⁻, LDA, THF; MeI, MeOH; NaHCO₃ (aq), CH₂Cl₂ (78%); (v) NaBH₄, CeCl₃, MeOH (95%); (vi) Cumene hydroperoxide, diisopropyl (-)-tartrate (cat), Ti(i-OPr)₄ (cat) (69%); (vii) 3,5-(O₂N)₂C₆H₃COCl, py, DMAP (87%).

Although 7 can be obtained by hydroboration-oxidation of commercial (R)-(-)- β -citronellene, the optical purity of this monoterpene was unsatisfactory for our purpose. Consequently, 7 was prepared by a known route from (R)-(+)-pulegone (5) via β -citronellic acid (6).⁴ After oxidation of 7 to citronellal (8), the enolate was alkylated with Eschenmoser's salt and the resulting amine was quaternized with methyl iodide then treated with base to give 9.⁵ Reduction of 9 in the presence of cerium trichloride⁶ gave the allylic alcohol 10 in an overall 50% yield from 6.

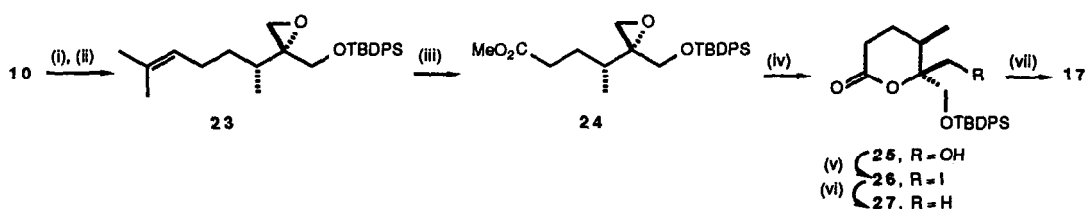
It was expected that asymmetric epoxidation⁷ of 10, catalyzed by diisopropyl (-)-tartrate,⁸ would afford 11, but, in fact, a 3:1 mixture of diastereomers 11 and 13 was obtained. The epoxides were separated as their 3,5-dinitrobenzoates (3,5-DNB) 12 and 14 by chromatography and crystalline 12 (mp 56.5-57 °C) was reduced to diol 15. After protection as the bis-3,5-DNB 16, the olefin was cleaved oxidatively with ruthenium(IV)⁹ and the esters were saponified. Acidification resulted in spontaneous lactonization to 17,¹⁰ the structure of which was confirmed by an x-ray crystallographic analysis.¹¹ Oxidation of this alcohol¹² afforded a carboxylic acid which was converted to methyl ester 18 with diazomethane.³ Introduction of the E ethylidene substituent via aldol condensation of 18 with acetaldehyde and elimination of the derived β -acetoxy lactone follows Narasaka's route in the racemic series.¹³ Saponification of 19 produced (+)-integerrinecic acid lactone (20)¹⁰ and esterification of this acid with 2-(trimethylsilyl)ethanol gave 21.¹ Hydrolytic opening of this δ -lactone yielded a hydroxy acid which was protected as its t-butyl dimethylsilyl ether 22. The latter was found to be identical in all respects to the substance prepared previously.³

The epoxide mixture obtained from 10 could be circumvented by employing the enantiomeric (+)-tartrate as catalyst,⁸ which furnished 13 and 11 in a 96:4 ratio respectively. After



(i) LiAlH_4 , THF (82%); (ii) 3,5-(O_2N) $_2\text{C}_6\text{H}_3\text{COCl}$, py, DMAP (87%); (iii) RuCl_3 (cat), NaIO_4 , K_2CO_3 , MeOH; 5% HCl, CHCl_3 (55%); (iv) RuCl_3 (cat), H_2IO_6 , CH_2N_2 (53%); (v) CH_3CHO , LDA, HMPA; Ac_2O , Et_3N ; DBU (50%); (vi) LiOH , THF- H_2O (1:1), 0°C (95%); (vii) $\text{Me}_3\text{Si}(\text{CH}_2)_2\text{OH}$, 2-chloro-1-methylpyridinium iodide, Et_3N (90%); (viii) LiOH , H_2O_2 , THF- H_2O (2:1) (57%); (ix) $t\text{-BuMe}_2\text{SiOSO}_2\text{CF}_3$, 2,6-lutidine, CH_2Cl_2 , 0°C; AcOH-THF- H_2O (3:3:1) (87%).

protection of 13 as its *t*-butyldiphenylsilyl (TBDPS) ether 23, the olefin was ozonized; oxidative work-up with Jones' reagent led to 24. Acid catalyzed opening of this epoxide was anchimerically assisted by the ester function¹⁴ to give 25, in which clean inversion had occurred at the quaternary center. The primary alcohol of 25 was reduced to a methyl group via iodide 26¹⁵ and removal of the silyl blocking group from 27 then yielded 17.



(i) Cumene hydroperoxide, diisopropyl (+)-tartrate (cat), $\text{Ti}(\text{i-OPr})_4$ (cat) (81%); (ii) $t\text{-BuPh}_2\text{SiCl}$, DMF, imidazole (90%); (iii) O_3 , CH_2Cl_2 , -78°C; CrO_3 , H_2SO_4 , Me_2CO , 0°C; CH_2N_2 (45%); (iv) $\text{CF}_3\text{CO}_2\text{H}$, CHCl_3 , -10°C (50%); (v) Ph_3P , I_2 , imidazole, C_6H_6 (90%); (vi) $n\text{-Bu}_3\text{SnH}$, AIBN; (vii) $n\text{-Bu}_4\text{NF}$, THF (60% from 26).

The stereoconvergent routes to integerrineic acid lactone elaborated above demonstrate that (*R*)- β -citronellol is a valuable chiral synthon for a principal subunit of 1. Studies in progress will determine whether this stratagem is applicable to other necic acids.

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REFERENCES

1. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. J. Am. Chem. Soc. **1984**, 106,
2. Niwa, H.; Miyachi, Y.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. Tetrahedron Lett. **1986**, 27, 4609.
3. White, J.D.; Ohira, S. J. Org. Chem. **1986**, 51, 5492.
4. Overberger, C.G.; Weise, J.K. J. Am. Chem. Soc. **1968**, 90, 3525.
5. Roberts, J.L.; Borromeo, P.S.; Poulter, C.D. Tetrahedron Lett. **1977**, 18, 1621.
6. Luche, J.L. J. Am. Chem. Soc. **1978**, 100, 2226.
7. Finn, M.G.; Sharpless, K.B. In Asymmetric Synthesis; Morrison, J.D., Ed.; Academic: Or1 Vol. 5, Chapter 8.
8. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. J. Am. Chem Soc. **1987**, 109, 5765.
9. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. J. Org. Chem. **1981**, 46, 3936
10. Niwa, H.; Miyachi, Y.; Uosaki, Y.; Yamada, K. Tetrahedron Lett. **1986**, 27, 4601.
11. Lactone 17 crystallized with orthorhombic symmetry in space group $P2_12_12_1$ with lattice constants $a = 6.909(2)$, $b = 7.455(1)$, and $c = 33.604(5)$ Å and two independent molecules per unit cell. Of 1398 independent reflections for $\theta < 57^\circ$, 1081 were considered to be observed [$I > 2.5 \sigma(I)$]. The structure was solved by a multiple solution procedure [Germain, G.; Main, P.; Woolfson, M.M. Acta Cryst. **1971**, A27, 368] and was refined by full-matrix least squares. The final discrepancy index was $R = 0.043$.
12. Chong, J.M.; Sharpless, K.B. J. Org. Chem. **1985**, 50, 1560.
13. Narasaka, K.; Uchimaru, T. Chem. Lett. **1982**, 57.
14. Ho, P.-T.; Davies, N. Synthesis **1983**, 462.
15. Edwards, M.P.; Ley, S.V.; Lister, S.G.; Palmer, B.D.; Williams, D.J. J. Org. Chem. **1984**, 49, 3503.

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