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Supplementary Material Available: Listing of spectral data for compounds in Schemes I and II (3 pages). Ordering information is given on any current masthead page.

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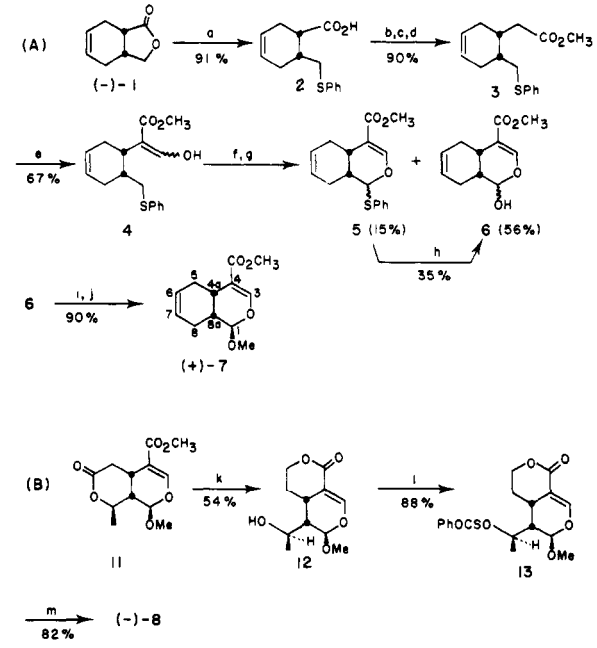
A General, Enantiospecific Synthesis of Cyclopentanoid Monoterpenes (Iridoids). The Total Synthesis of (−)-1-*O*-Methylsweroside Aglucon

Summary: A total synthesis of optically active cyclopentanoid monoterpenes (iridoids) can be achieved by using (−)-(1*S*,5*R*)-*cis*-3-oxabicyclo[4.3.0]non-7-en-2-one (1) to prepare a key bicyclic synthon, (+)-7. The generality and enantiospecificity of this approach is demonstrated by the preparation of (−)-1-*O*-methylsweroside aglucon (8).

Sir: The natural products known as cyclopentanoid monterpenes,[1] or iridoids,[2] are widely distributed in plants and are important for the biosynthesis of some types of indole alkaloids.[3] Because of this and the interest in those iridoids which have significant biological activity,[4] several research groups have pursued the synthesis of these natural products during the past 20 years.[1a,5] The inherent strategies have led to efficient and stereospecific total syntheses of many different iridoids[6] but cannot be adapted easily to the synthesis of structural analogues for use in biological studies and do not result in the correct absolute configuration in most cases. Four of the five previous syntheses of optically active iridoids involved resolution of racemic intermediates[6j] or lacked complete regio- and stereochemical control even when there was a high degree of asymmetric induction.[6h,cc,dd] We now report a general solution to the problem of synthetic versatility and enantiospecificity for the iridoids as exemplified by a synthesis of (−)-1-*O*-methylsweroside aglucon (8).[7]

The synthesis of (−)-8 employs (−)-(1*S*,5*R*)-*cis*-3-oxabicyclo[4.3.0]non-7-en-2-one (1), which can be produced on

Scheme I[a]



[a] (a) LiSPh, 1.05 equiv; DMF; reflux; 4 h. (b) $(COCl)_2$; C_6H_6; room temperature, 1.5 h. (c) CH_2N_2; Et_2O; room temperature, 4 h. (d) Ag_2O, catalyst; MeOH; reflux, 20 min. (e) LDA, 1.05 equiv; THF; −50 °C, 1 h; then HCO_2Et, 1.5 equiv; −50 °C, 1 h. (f) $NaIO_4$, 1 equiv; MeOH:THF:H_2O (6:3:4); room temperature, overnight. (g) 2,6-Lutidine, TFAA, 3 equiv; CH_3CN; −15 to 0 °C, 1 h. (h) $HgCl_2$, 3 equiv; CH_3CN:H_2O (3:1); reflux; 20 h. (i) BF_3; OEt_2; MeOH; 1 h, room temperature. (j) Allyl *O*-Me_3Si (excess); Tf-*O*-Me_3Si (catalyst); CH_2Cl_2, −20 to 0 °C, 3 h. (k) $NaBH_4$, 4 molar equiv; *i*-PrOH:H_2O (10:1); 0 to 15 °C, 6 h. (l) PhOC(S)Cl, DMAP, 2 equiv; CH_3CN:C_5H_5N (3:1); 80 °C, 3 h. (m) 170 °C, 20 min, N_2.

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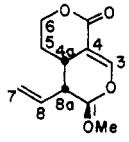
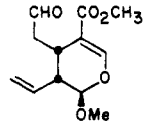
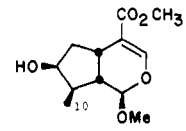
a preparative scale in excellent yield and optical purity by the enzymatic in vitro oxidation of (±)-*cis*-4,5-bis(hydroxymethyl)cyclohexene,[8] to provide the correct absolute configuration at two of the three asymmetric centers of 8. A key bicyclic synthon, (+)-7, can be prepared by two one-carbon homologations and an intramolecular Pummerer reaction from lactone 1 in good overall yield as described below. This key compound was used by us earlier, in racemic form, for total syntheses of the *O*-methyl acetals of the iridoid aglucons, sweroside (8),[6t] secologanin (9),[6t] loganin (10),[6w] and 10-hydroxyloganin[6w]; therefore, it meets the versatility requirement. We show now that it also satisfies the absolute stereochemistry requirement by its conversion to (−)-8.



8



9



10

The use of (−)-1 to synthesize (+)-7 required chemical transformations that did not alter the absolute configuration at C-1 and C-5 of 1 since these positions have the same absolute stereochemistry as the bridgehead carbons in almost all iridoids.[1] Experimentation showed that the reaction sequence drawn in Scheme I, route A, met this requirement best even though it required two separate one-carbon homologations. Nevertheless, the yields of both steps were good to excellent. The only step having a moderate yield was the intramolecular Pummerer reaction (4 → 6), which gave a byproduct (5) that could be transformed to 6 for a combined overall yield of 33% from (−)-1. Conversion of 6 to its *O*-methyl acetal, (+)-7,[9] gave the key synthon with the required absolute stereochemistry at its three asymmetric carbons.

By our previously described methods[6t] (+)-7 was converted in good yield to (−)-8 (eq 1): $[\alpha]_D$ −219° (*c* 0.80, $CHCl_3$); $[\theta]_{240\,nm}$ -2.0×10^4; all other spectral characteristics were the same as those of (±)-8.[6t]

$$(+)\text{-}7 \xrightarrow[\text{ref 6t}]{\text{6 steps}} (-)\text{-}8 \qquad (1)$$

Since natural (−)-8 was unknown and could not be prepared simply from sweroside aglucon[7] because of structural rearrangement or epimerization,[10] a sample for comparison was made from natural (−)-loganin[11] via the *O*-methyl acetal lactone 11[12] as shown in Scheme I, route B. Reduction of 11 with $NaBH_4$ and dehydration[13] of 12 by pyrolysis of its phenylthiocarbonate 13 gave the authentic sample of (−)-1β-8: $[\alpha]_D$ −209° (*c* 0.55, $CHCl_3$); $[\theta]_{239\,nm}$ -1.9×10^4. The IR, ^1H NMR, and MS spectral data were identical for the synthetic and natural samples as expected.

The work we describe here represents the first general enantiospecific synthesis of a secoiridoid aglucon and is a formal synthesis of one other secoiridoid (9) and two iridoid (10 and its 10-hydroxy derivative) aglucons. Our strategy complements the biomimetic synthesis of optically active sweroside and secologanin aglucon *O*-methyl acetals described by L.-F. Tietze and co-workers[6p] and could be used for the synthesis of (−)-loganin[6j,11] and (−)-sarracenin[6cc,ff] by known methods. Perhaps of equal importance, it has sufficient versatility for the preparation of numerous iridoid structural analogues as part of a research program to study the reasons for the antibacterial[4e] and antitumor[4c,d] activity of certain naturally occurring iridoids.

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Supplementary Material Available: Full experimental and spectral details for compounds 1-7, 12, and 13 (7 pages). Ordering information is given on any current masthead page.

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(9) The yield of (±)-1β-*O*-Me-7 was 55% (and the 1α epimer, 39%) when (+)-6 was treated with *p*-TsOH in MeOH at room temperature for 18 h (M. Nakane, Ph.D. Dissertation, Tokyo Institute of Technology, 1980). The conditions used with optically active 6 gave the highest ratio of (+)-1β-*O*-Me-7 to (+)-1α-*O*-Me-7 (7:1).

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Stereoselectivity in Intramolecular Amidomercuration. Kinetic vs. Thermodynamic Control[1]

Summary: Stereoselective mercuric ion initiated cyclofunctionalization of δ-alkenylcarbamate 1 requires conditions which do not lead to equilibration [$Hg(OAc)_2$ in THF], while stereoselective cyclization of the ε-alkenylcarbamate 2 is observed only under conditions which do lead to equilibration [$Hg(O_2CCF_3)_2$ in nitromethane, 20 h].

Sir: Recent studies in several laboratories have demonstrated the potential synthetic utility of electrophile-initiated cyclizations of amide and carbamate derivatives of unsaturated amines.[2-5] One critically important feature in the application of these reactions to the synthesis of

(1) This paper constitutes paper 3 in the series Applications of Intramolecular Amidomercuration. For paper 2, see ref 2a. We have applied the term amidomercuration to cyclizations involving either amide or carbamate functionalities.[2] Others[3a,b] have utilized the term ureidomercuration for cyclizations involving carbamates even though rules of nomenclature indicate that "ureido" applies to the NH_2CONH- group: Rule C-971.2, IUPAC Rules for Nomenclature of Organic Compounds. See: Riguady, J.; Klesney, S. P. "Nomenclature of Organic Chemistry; Sections A, B, C, D, E, F, and H; 1979 Edition"; Pergamon Press: New York, 1979; p 297.

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