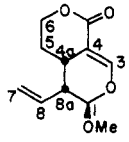
a preparative scale in excellent yield and optical purity by the enzymatic in vitro oxidation of (±)-*cis*-4,5-bis(hydroxymethyl)cyclohexene,[8] to provide the correct absolute configuration at two of the three asymmetric centers of 8. A key bicyclic synthon, (+)-7, can be prepared by two one-carbon 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.



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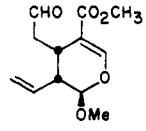

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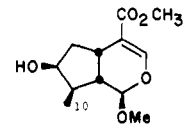

10

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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(8) Jakovic, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659. This compound also has been prepared by the following groups using a different method based on enantiotropic hydrolysis of methyl esters with pig liver esterase: Schneider, M.; Engel, N.; Hönicke, P.; Heinemann, G.; Görisch, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 67. Gais, H.-J.; Lukas, K. L. *Ibid.* **1984**, *23*, 142.

(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).

(10) Treatment of (−)-sweroside with β-glucosidase in 0.02 M citrate buffer (pH 5) for 18 h at room temperature gives its 8a-epi aglucon with the 8a(*S*) (*H*-4a, *H*-8a trans): Ikeda, T.; Hutchinson, C. R.; Meier, H.; Tietze, L.-F. *Tetrahedron Lett.* **1984**, *25*, 2427.

(11) Sheth, K.; Ramstad, E.; Wolinsky, J. *Tetrahedron Lett.* **1961**, 394. Battersby, A. R.; Hall, E. S.; Southgate, R. *J. Chem. Soc. C.* **1969**, 721.

(12) Nakane, M.; Hutchinson, C. R.; VanEngen, D.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 7079.

(13) We used the procedures of H. Gerlach and W. Müller (*Helv. Chim. Acta* **1972**, *55*, 2277) and M. J. Robins and J. S. Wilson (*J. Am. Chem. Soc.* **1981**, *103*, 932) for dehydration of 12, since all other methods gave only the isomeric 8,8a-trisubstituted olefin.

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.

(2) (a) Harding, K.; Burks, S. R. *J. Org. Chem.* **1984**, *49*, 40-44. (b) Harding, K. E.; Burks, S. R. *Ibid.* **1981**, *46*, 3920-3922.

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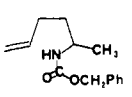
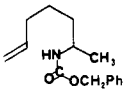
complex natural products is the stereoselectivity of such reactions. The observation that mercuric ion initiated cyclization of δ-alkenylcarbamate **1** proceeds with high



1



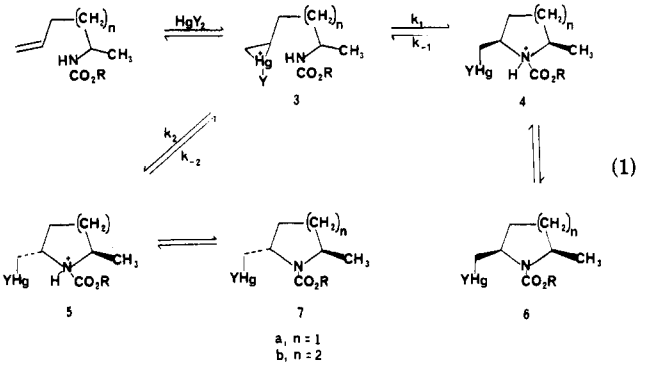
2

stereoselectivity[2b,3a] but that cyclization of the same substrate effected with an electrophilic selenium reagent is totally nonselective[3b] illustrates the lack of understanding in this area. Our studies into intramolecular amidomercuration of carbamates **1** and **2** have now shown that the stereoselectivity of these cyclizations can be critically dependent upon whether the reaction conditions result in kinetic or thermodynamic control of the products. Stereoselective cyclization of δ-alkenylcarbamate **1** requires conditions giving kinetic control, while stereoselective cyclization of ε-alkenylcarbamate **2** is observed only under equilibrating conditions.

The mercuric ion initiated cyclizations of free amines related to **2** have been reported to produce 2,6-disubstituted piperidines in moderate yield as a mixture of cis and trans isomers.[6] The cyclization, with phenylselenyl chloride, of a carbamate related to **2** has been reported by Clive[5] to give the cis-disubstituted piperidine product in excellent yield and stereoselectivity. However, we found that treatment of carbamate **2**[8] with mercuric acetate in tetrahydrofuran followed by reduction of the carbon–mercury bond gave a mixture (ca. 60:40) of *trans*- and *cis*-*N*-(carbobenzyloxy)-2,6-dimethylpiperidines.[9] Similar results were obtained with mercuric acetate in other solvents. After considerable experimentation, we found that stereoselective cyclization could be effected by reaction with mercuric trifluoroacetate in nitromethane for a period of 20–24 h. Reduction[10] of the carbon–mercury bond gave a 93% yield of *cis*-*N*-(carbobenzyloxy)-2,6-dimethylpiperidine containing less than 2% of the trans isomer.[12]

The progress of the reaction was followed by ^{1}H NMR (CD_3NO_2 solvent) to show that the stereoselectivity of this reaction is a result of equilibrium control. The ^{1}H NMR spectrum of carbamate **2** immediately after treatment with mercuric trifluoroacetate shows the complete disappearance of the signals for the starting material. The presence of a mixture is indicated by the presence of two slightly separated methyl doublets (at a chemical shift quite distinct from the methyl signal of the starting material) and two signals for the methine protons. Reduction of the organomercurial intermediate after a short reaction time gave a mixture of cis and trans products. If the reaction was allowed to continue, one set of doublets decreased as did one of the signals for methine protons. The rate of equilibration was shown to be dependent upon both the mercuric salt used and the solvent. Cyclization with mercuric acetate in nitromethane gave a mixture even after a reaction period of several days. Mercuric trifluoroacetate in deuteriochloroform gave an organomercurial which equilibrated to the cis product almost exclusively, but only over a several-day period. If trifluoroacetic acid was added to the mixture of organomercurials obtained by cyclization with mercuric acetate, equilibration to the cis product occurred at a rate that was dependent upon the amount of acid added.

These results clearly show that the initial cyclofunctionalization reaction of **2** with mercuric ion is nonstereoselective (giving a mixture of cis and trans products, $k_1 \approx k_2$ in eq 1), but that under conditions favoring equilibration, conversion of the trans product **7b** into the cis product **6b** occurs. Although the factors controlling relative stability of the cis and trans isomers of the cyclofunctionalization products in this reaction are not easily defined, it is reasonable to assume that A$^{(1,3)}$-type strain involving the carbamate functionality and the substituents at C-2 and C-6 is an important contributor.[13,14]



(1)

Although our earlier studies with the δ-alkenylcarbamate **1** had shown no changes in product ratios (trans:cis = 98:2) under the conditions examined at that time, the above results as well as Danishefsky's observation that cyclization of **1** with *N*-(phenylselenyl)phthalimide gave a 1:1 mixture of cis and trans products[3b] led us to examine the cyclization of **1** with mercuric trifluoroacetate in trideuterionitromethane. The ^{1}H NMR spectrum immediately after addition of mercuric trifluoroacetate showed the presence of one major methyl doublet. Over a period of time a second doublet developed in the spectrum. After a period of 9 days, the two doublets were present in a ratio of 70:30 with the new signal predominating. The ratio of these signals

(3) (a) Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Tetrahedron Lett.* **1983**, *24*, 11–14. (b) Webb, R. R., II; Danishefsky, S. *Ibid.* **1983**, *24*, 1357–1360. (c) Danishefsky, S.; Taniyama, E. *Ibid.* **1983**, *24*, 15–18.

(4) (a) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233–3235. (b) Aida, T.; Legault, R.; Dugat, D.; Durst, T. *Tetrahedron Lett.* **1979**, 4993–4994. (c) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330–336.

(5) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120–2126.

(6) Moriyama, Y.; Doan-Huynh, D.; Monneret, C.; Khuong-Huu, Q. *Tetrahedron Lett.* **1977**, 825–828. See also ref 7.

(7) Barluenga, J.; Najera, C.; Yus, M. *Synthesis* **1979**, 896–898.

(8) (a) The carbamate **2** was prepared from 6-hepten-2-one by conversion to the oxime, reduction with lithium aluminum hydride, and in situ reaction of the amine with benzyl chloroformate.[2b] (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863–869.

(9) Authentic *cis*-*N*-(carbobenzyloxy)-2,6-dimethylpiperidine was prepared by reaction of *cis*-2,6-dimethylpiperidine (Aldrich) with benzyl chloroformate.

(10) The reduction was effected by removal of nitromethane under vacuum, dissolution of the organomercurial in methylene chloride, treatment with sodium hydroxide solution in the presence of tetrabutylammonium hydroxide,[11a] and, then, addition of basic sodium borohydride solution. The initial treatment with base and phase-transfer reagent was necessary to avoid production of major amounts of starting carbamate during the reduction.[11] This type of problem has been observed previously in the reduction of aminomercuration products.[6,11]

(11) (a) Benhamou, M. C.; Etemad-Moghadam, G.; Speziale, V.; Lattes, A. *Synthesis* **1979**, 891–892. (b) Barluenga, J.; Najera, C.; Yus, M. *Ibid.* **1978**, 911–914. (c) Griffith, R. C.; Gentile, R. J.; Davidson, T. A.; Scott, F. L. *J. Org. Chem.* **1979**, *44*, 3580–3583.

(12) As determined by HPLC analysis on 10-μm Spherisorb and by ^{1}H NMR at 200 MHz.

(13) Johnson, R. A. *J. Org. Chem.* **1968**, *33*, 3627–3632.

(14) The cis product **6b** can maintain overlap of the nitrogen lone pair with the carbamate carbonyl in a conformation with both C-2 and C-6 substituents axial (known to be the lowest energy conformation in related amides[13]) while the trans product **7b** must have either the C-2 or C-6 substituent equatorial, forcing the carbamate out of overlap with the nitrogen lone pair. This results in an increase in energy of this isomer and increases the basicity of the nitrogen toward protonation to regenerate intermediate **5b**. Protonation of the carbonyl oxygen with the carbonyl group orthogonal to the nitrogen lone pair would give an intermediate capable of reversal to starting material also.

did not change significantly on further standing. Reduction of the organomercurial at this time gave a mixture of *cis*- and *trans*-*N*-(carbobenzyloxy)-2,5-dimethylpyrrolidine with the cis isomer **6a** predominating! The equilibration of the organomercurials could be effected in only 2 days by the addition of 3 equiv of trifluoroacetic acid. Thus, equilibration of the initial cyclofunctionalization product can be observed in this case, although the rate is much slower than in the case of **2** and the equilibrium ratio is not as high.

Thus, there is a clear divergence of behavior between the δ-alkenylcarbamate **1** (kinetic stereoselectivity and thermodynamic nonselectivity) and the ϵ-alkenylcarbamate **2** (kinetic nonselectivity and thermodynamic stereoselectivity). This study clearly shows for the first time that the choice of reaction conditions can be critically important to the stereoselectivity observed in mercuric ion initiated cyclofunctionalization of unsaturated carbamates (intramolecular amidomercuration).[15,16]

(15) For examples of the importance of equilibration in the stereoselective cyclofunctionalization of unsaturated systems with oxygen nucleophiles (involving electrophiles other than mercuric ion), see inter alia: Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829–4830. Bartlett, P. A.; Myerson, J. *Ibid.* **1978**, *100*, 3950–3952. Rychnovsky, S.; Bartlett, P. A. *Ibid.* **1981**, *103*, 3963–3964. Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013–4018. Bartlett, P. A. In "Asymmetric Synthesis"; Morrison, J. D., Ed; Academic Press: New York, **1983**; Vol 3, Chapter 6 and references cited therein.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectral data for structures **2**, **6b** and **7b**, **7a** and **6a**, and *N*-(carbobenzyloxy)-2,6-dimethylpiperidine (2 pages). Ordering information is given on any current masthead page.

(16) **Note added in proof**: The regiochemistry of aminomercuration reactions of *cis,cis*-1,5-cyclooctadiene has been shown to be dependent upon the nature of the mercuric salt employed: Barluenga, J.; Pérez-Prieto, J.; Bayón, A. M.; Asensio, G. *Tetrahedron* **1984**, *40*, 1199–1204.

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