both RCL and LCL. IIa was irradiated at 310, 335, 370, and 400 nm, and IIb at 370 nm. The samples were evaporated to dryness and refluxed for 2 hr in 10 ml of chloroform with 10 mg of 3-chloroperbenzoic acid, which was then shaken with 100 ml of aqueous 1 *N* NaOH. The solvent was evaporated and the residue was taken up in 2 ml of warm benzene, and chromatographed on neutral aluminum oxide with benzene as eluent. This procedure eliminated all of the remaining olefin, allowing for accurate determination of the helicene concentration.

Acknowledgments. The authors wish to acknowledge the National Science Foundation for a graduate scholarship for William J. Bernstein. Part of this research was sponsored by the U. S. Atomic Energy Commission which is gratefully acknowledged.

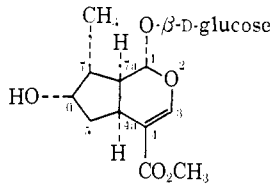
Asymmetric Synthesis of Loganin. Stereospecific Formation of (1*R*,2*R*)- and (1*S*,2*S*)-2-Methyl-3-cyclopenten-1-ol and (2*R*)- and (2*S*)-2-Methylcyclopentanone

John J. Partridge,* Naresh K. Chadha, and Milan R. Uskoković

Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received July 27, 1972*

Abstract: A short asymmetrically induced synthesis of loganin pentaacetate (**6**) has been completed. 5-Methylcyclopentadiene (**7**) underwent a highly selective reaction with (+)-di-3-pinanylborane to yield (1*R*,2*R*)-2-methyl-3-cyclopenten-1-ol (**8a**) of 95% minimum optical purity. (−)-Di-3-pinanylborane gave (1*S*,2*S*)-2-methyl-3-cyclopenten-1-ol (**8b**) of equivalent optical purity. The absolute configurations of alcohols **8a** and **8b** were determined by their conversion into the previously unknown (2*R*)- and (2*S*)-2-methylcyclopentanones (**12a** and **12b**) and measuring the ORD and CD spectra of these ketones. The 1*R*,2*R* alcohol **8a** afforded the optically active methanesulfonate **10** which was converted into the 1*S*,2*R* acetate **2** with tetraethylammonium acetate. Irradiation of a 10:1 mixture of acetate **2** and methyl diformylacetate (**3**) gave the desired loganin aglucone derivative **5** regioselectively. Treatment of **5** with 2,3,4,6-tetra-*O*-acetyl-β-D-glucose and boron trifluoride afforded loganin pentaacetate (**6**) which has been converted to loganin (**1**).

The iridoid glucoside loganin (**1**) occupies a central position in the biosynthesis[1] of the *Corynanthe*,[2]



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Aspidosperma,[2] *Iboga*,[2] *Ipecacuanha*,[3] and *Cinchona*[4] groups of indole alkaloids. Evidence to date indicates that loganin becomes the "C_9–C_{10}" nontryptamine moiety incorporated into the skeleton of these alkaloids.[1] Tracer experiments also show that loganin is a biogenetic precursor of a growing number of iridoids,[5] alkaloid glucosides,[6] and monoterpene alkaloids.[7]

Loganin was first isolated from the fruit pulp of *Strychnos nux vomica*.[8] It occurs in other *Strychnos* species as well as in the water plant *Menyanthes trifoliata* and in *Vinca rosea*.[2] More recently, loganin has been detected in various species of *Gentiana* (*Gentianaceae*),[5] *Hydrangea* (*Saxifragaceae*),[9] *Lonicera* (*Caprifoliaceae*),[9] *Mytragyna* (*Rubiaceae*),[10] and *Swertia* (*Gentianaceae*).[11] Thus, loganin appears to be an important building block in much of the plant world.

The structure and stereochemistry of loganin (**1**) have been the subject of many reports since its discovery in 1884 by Dunstan and Short.[8] The correct structure was postulated by Wolinsky[12] in 1961, but the structure and stereochemistry were not firmly established until 1968 when three groups[13] independently announced corroborating evidence for absolute structure **1**. This structure has since been confirmed by X-ray analysis,[14]

(1) For recent reviews, see: O. Sticher, *Pharm. Acta Helv.*, **44**, 453 (1969); E. Leete, *Accounts Chem. Res.*, **2**, 59 (1969); A. I. Scott, *ibid.*, **3**, 151 (1970); A. R. Battersby in "The Alkaloids," Vol. 1, J. E. Saxton, Ed. (Specialist Periodical Reports), The Chemical Society, London, 1971, pp 31–47.

(2) A. R. Battersby, E. S. Hall, and R. Southgate, *J. Chem. Soc. C*, 721 (1969), and references cited therein.

(3) A. R. Battersby and B. Gregory, *Chem. Commun.*, 134 (1968); A. R. Battersby and R. J. Parry, *ibid.*, 901 (1971).

(4) A. R. Battersby and E. S. Hall, *ibid.*, 194 (1970); A. R. Battersby and R. J. Parry, *ibid.*, 30, 31 (1971).

(5) H. Inouye, S. Ueda, and Y. Takeda, *Tetrahedron Lett.*, 3351 (1970); 4069, 4073 (1971), and references therein; H. Inouye, *Pharmacogn. Phytochem. Int. Congr.*, **1**, 290 (1970).

(6) A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc. C*, 1187, 1193 (1969).

(7) D. Gross in "Fortschritte der Chemie Organischer Naturstoffe," Vol. 28, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1970, pp 140–143.

(8) W. R. Dunstan and F. W. Short, *Pharm. J. Trans.*, **14**, 1025 (1884).

(9) V. Plouvier, *C. R. Acad. Sci.*, **258**, 3919 (1964).

(10) D. S. Bhakuni and R. S. Kapil, *Experientia*, **24**, 1185A (1968).

(11) C. J. Coscia, L. Botta, and R. Guarnaccia, *Arch. Biochem. Biophys.*, **136**, 498 (1970).

(12) K. Sheth, E. Ramstad, and J. Wolinsky, *Tetrahedron Lett.*, 394 (1961).

(13) A. R. Battersby, R. S. Kapil, and R. Southgate, *Chem. Commun.*, 131 (1968); S. Brechbühler-Bader, C. J. Coscia, P. Loew, Ch. von Szczepanski, and D. Arigoni, *ibid.*, 136 (1968); H. Inouye, T. Yoshida, and S. Tobita, *Tetrahedron Lett.*, 2945 (1968).

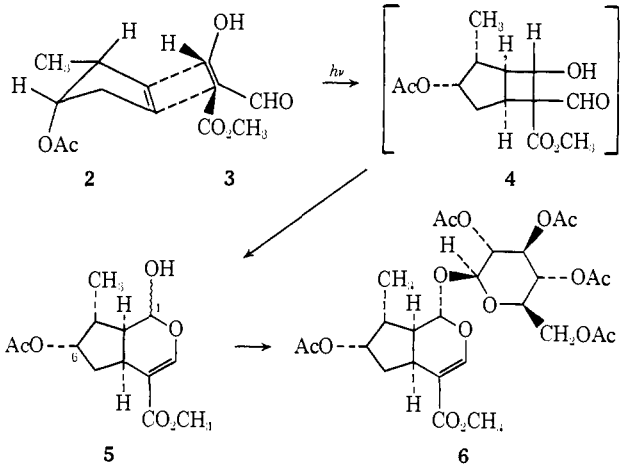
(14) P. J. Lentz, Jr., and M. G. Rossmann, *Chem. Commun.*, 1269 (1969).

by the partial synthesis of Inouye,[15] and by the total synthesis of Büchi.[16]

Our interest in the iridoid glucosides[17] stemmed from reports that a number of these substances and their biogenetic products possess biologically attractive properties. Whereas the biological activity of loganin has not been firmly established,[18] this substance nevertheless represented a synthetic challenge. Additionally, loganin is a potential precursor of the biogenetically important substance secologanin.[19]

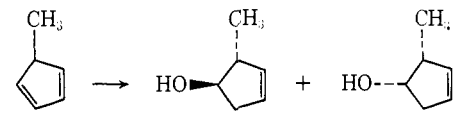
Our synthetic plan is outlined in Scheme I and

Scheme I



makes use of the enone photoannelation reaction of a β-tricarbonyl compound as described by Büchi and coworkers.[16,20] We anticipated that photoannelation would occur regioselectively with the enol **3** attacking the less hindered face of optically active olefin **2** to give the primary photoproduct **4**. This cyclobutane derivative, formed by a cis 2 + 2 addition, would be expected to undergo retro-aldol cleavage to form the corresponding 1,5-dialdehyde derivative, which would cyclize to hemiacetal **5**. Asymmetric induction during the photoreaction should occur to give the loganin aglucone derivative **5** with the proper absolute configuration at a minimum of four of the five asymmetric centers needed for the synthesis of loganin. In addition the C-6 hydroxy group would be protected as the acetate and the C-1 hemiacetal function would be free to undergo glucosidation to complete the synthesis. Thus, a workable preparation of 1*S*,2*R* acetate **2** was needed.

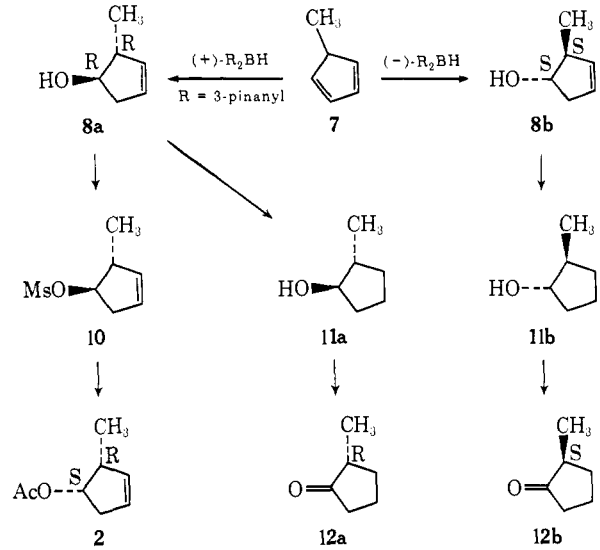
Cyclopentadienylsodium was alkylated with methyl iodide at −78° in tetrahydrofuran to form the thermally labile 5-methylcyclopentadiene (**7**).[21] This reactive intermediate is known to isomerize readily at 0° to a 1:1 mixture of 1- and 2-methylcyclopentadienes and can also undergo Diels–Alder additions.[21] For these reasons diene **7** was not isolated but was immediately treated with borane in tetrahydrofuran at −78° to yield, upon hydrogen peroxide oxidation, a 9:1 mixture of alcohols **8** and **9**.[22] These results indicated that the methyl group in diene **7** directed borane attack mainly to the opposite face of the ring. None of the corresponding allylic alcohols were detected, although considerable high boiling materials (diols, diene dimers) were obtained.



The stereochemistry of the homoallylic alcohols was assigned by inspection of molecular models and by chemical transformations. The major alcohol **8** was catalytically hydrogenated to the corresponding saturated alcohol, which was identical in all respects with *trans*-2-methylcyclopentan-1-ol independently prepared either by hydroboration–oxidation of 1-methylcyclopentene[23] or by diborane reduction of 2-methylcyclopentanone.[24] The saturated alcohol, obtained from **9** upon hydrogenation, was identical spectrally with *cis*-2-methylcyclopentan-1-ol formed on reduction of 2-methylcyclopentanone with disiamylborane.[24]

Once the mode of borane attack on 5-methylcyclopentadiene (**7**) was established, studies on asymmetric hydroboration were initiated. Di-3-pinanylborane is one of the most selective hydroboration agents known and has been reported to induce a very high degree of asymmetry with certain olefins.[25] When diene **7** was treated with (+)- or (−)-di-3-pinanylborane at −78° in concentrated solutions, the trans alcohols **8a**, $[\alpha]^{25}D$ −169°, and **8b**, $[\alpha]^{25}D$ +170°, were each obtained in over 30% yield (Scheme II). None of the corresponding cis alcohol **9** or allylic alcohols were detected. To check the amount of asymmetric induction ob-

Scheme II



(15) H. Inouye, T. Yoshida, S. Tobita, and M. Okigawa, *Tetrahedron*, **26**, 3905 (1970).

(16) G. Büchi, J. A. Carlson, J. E. Powell, Jr., and L.-F. Tietze, *J. Amer. Chem. Soc.*, **92**, 2165 (1970).

(17) J. M. Bobbitt and K.-P. Segebarth in "Cyclopentanoid Terpene Derivatives," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1969, pp 1–145.

(18) Loganin has been used in folk medicine as a bitter tonic; *cf.* R. Hegnauer, *Pharm. Acta Helv.*, **41**, 577 (1966).

(19) See J. J. Partridge, N. K. Chadha, S. Faber, and M. R. Uskoković, *Synth. Commun.*, **1**, 233 (1971), for one approach to secologanin.

(20) P. de Mayo, *Accounts Chem. Res.*, **4**, 41 (1971).

(21) V. A. Mironov, E. V. Sobolev, and A. N. Elizarova, *Tetrahedron*, **19**, 1939 (1963); S. McLean and P. Haynes, *ibid.*, **21**, 2313, 2329, 2343 (1965).

(22) The interconversion of alcohols **8** and **9** was carried out *via* mesylate **10** and acetate **2**; see Experimental Section for details.

(23) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).

(24) H. C. Brown and D. B. Bigley, *ibid.*, **83**, 3166 (1961).

(25) *Cf.* J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 220–241.

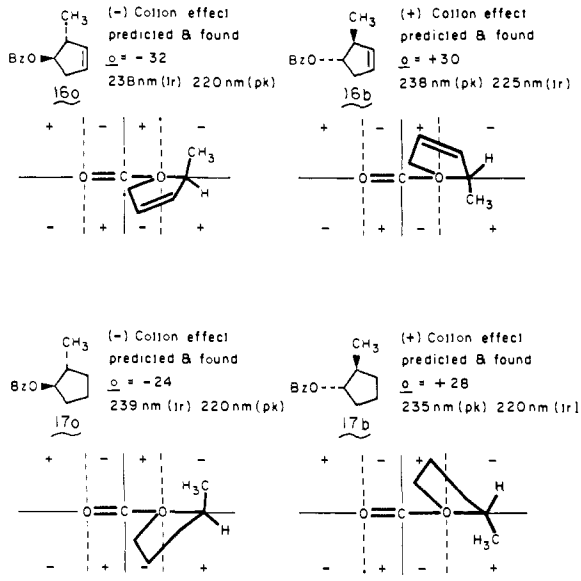


Figure 1. The benzoate sector for *trans*-2-methyl-3-cyclopenten-1-ol derivatives.

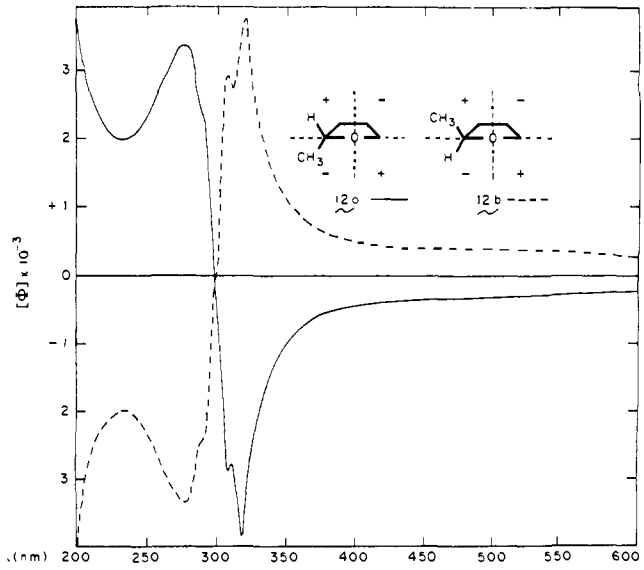


Figure 2. ORD spectra of ketones **12a** and **12b** in dioxane.

tained by these hydroborating agents, racemic alcohol **8** was resolved into its antipodes **8a** and **8b** as follows. The racemic acid phthalate **13** was treated with (+)-α-methylbenzylamine affording the salt of **13a**, $[\alpha]^{25}D$ −71° on repeated crystallization. The crystallization mother liquors were converted back into the free acid phthalate, which was treated with (−)-α-methylbenzylamine to yield the enantiomeric salt which exhibited $[\alpha]^{25}D$ +71°. These salts were converted into the acid phthalates **13a** and **13b** from which the resolved alcohols **8a**, $[\alpha]^{25}D$ −175°, and **8b**, $[\alpha]^{25}D$ +174°, were regenerated. To determine if complete resolution had been effected, the alcohols were transformed into the liquid diastereomeric esters **14** and **15** with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[26] These (+)-α-methoxy-α-trifluoromethylphenylacetates (MTPA) exhibited different chemical shifts for the C-2 methyl groups and the allylic hydrogens in the proton nmr spectra. On the basis of the 100-MHz nmr spectra of these esters, alcohol **8a** was shown to be at least 99% optically pure and alcohol **8b** at least 98% optically pure.

13a, R = $COC_{11}H_{11}CO_2H$ **13b**, R = $COC_{11}H_{11}CO_2H$

14, R = (+)-MTPA **15**, R = (+)-MTPA

The hydroboration product from (+)-di-3-pinanylborane (mainly **8a**) was esterified with the aforementioned optically active acid chloride.[26] The 100-MHz nmr spectrum of the ester **14** indicated a minimum optical purity of 95%. Likewise, the ester **15** derived from the (−)-di-3-pinanylborane hydroboration product (mainly **8b**) was shown to be at least 96% optically pure. Thus, the hydroboration–oxidation reaction with (+)- and (−)-di-3-pinanylborane gave acceptable yields of highly optically pure trans alcohols **8a** and **8b** uncontaminated by cis alcohol **9**.

(26) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); J. A. Dale, Ph.D. Thesis, Stanford University, 1970.

It became imperative to determine the absolute configurations of these alcohols. Toward this end, the alcohols **8a** and **8b** and their hydrogenation products **11a** and **11b** were converted into the corresponding benzoates, and the ORD and CD spectra of these esters were obtained. Using the benzoate sector rule,[27] the esters **16a**, **16b**, **17a**, and **17b** were assigned the absolute configurations shown in Figure 1. These assignments were confirmed by the ORD and CD spectra of the enantiomeric 2-methylcyclopentanones (**12a** and **12b**) which were synthesized for the first time.[28] These ketones were obtained by brief exposure of alcohols **11a** and **11b** to standard Jones reagent.[29] Reexposure of ketones **12a** and **12b** to the oxidation media did not alter the observed optical rotations of these substances. Although the neat ketones were optically stable over a 1-month period, methanolic solutions of these ketones partially racemized on standing at room temperature for 1 day. The addition of a catalytic amount of sodium methoxide to these solutions resulted in complete racemization in seconds. As a further check on the optical rotation values, ketone **12b** was reduced with lithium aluminum hydride in ether and the major reduction product **11b**, $[\alpha]^{25}D$ +41.7°, was isolated by preparative gas chromatography. The optical rotation of this alcohol sample indicated that only *ca.* 5% racemization had taken place during the oxidation–reduction sequence (**11b** → **12b** → **11b**) since the pure alcohol **11b** exhibited a rotation of $[\alpha]^{25}D$ +43.9°.

The ORD spectra of ketones **12a** and **12b** (Figure 2) constituted definitive proof for the absolute stereochemistry shown in Scheme II. Ketone **12a** exhibited a strong negative Cotton effect and was assigned the 2*R* absolute configuration. Conversely,

(27) *Cf.*, N. Harada, M. Ohashi, and K. Nakanishi, *J. Amer. Chem. Soc.*, **90**, 7349 (1968), and references therein.

(28) Several published reports have incorrectly implied that the optically active forms of 2-methylcyclopentanone have been prepared and characterized. See J. D. Morrison and H. S. Mosher, ref 25, p 231; J. Fried, C. Lin, M. Mehra, W. Kao, and P. Dalven, *Ann. N. Y. Acad. Sci.*, **180**, 38 (1971); J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, *J. Amer. Chem. Soc.*, **94**, 4342 (1972).

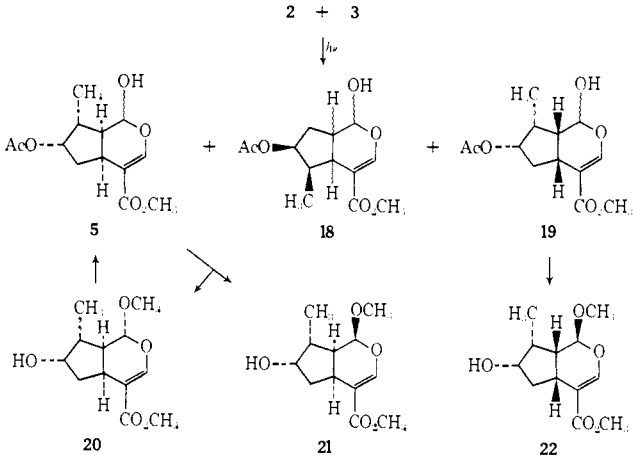
(29) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

ketone **12b** showed a strong positive Cotton effect and was assigned the 2*S* absolute configuration.[30]

To form the desired cis acetate **2**, we required a means of inverting the C-1 configuration of alcohol **8a**. The inversion sequence was first studied with alcohol **8** which afforded the racemic mesylate **10** quantitatively. This unstable substance yielded little inverted alcohol **9** or acetate **2** using a variety of conditions. Instead, a mixture of olefinic materials was always obtained. However, a modification of the method of Cope and Nealy[31] employing tetraethylammonium acetate in 1:1 hexamethylphosphoramide–acetone afforded racemic acetate **2** as the major product. The pure acetate was obtained by careful fractional distillation in 63% yield. It is noteworthy that no trans acetate was formed. Thus, the conversion of mesylate **10** to acetate **2** probably occurred by a displacement reaction without anchimeric assistance of the homoallylic double bond.[32] For the preparation of loganin pentaacetate (**6**), optically active alcohol **8a** was transformed quantitatively into the corresponding optically active methanesulfonate derivative **10**. This substance afforded 1*S*,2*R* acetate **2** in 60% yield on treatment with tetraethylammonium acetate as described above.

The key photochemical ring annelation reaction[16] (*cf.* Scheme I) was also first carried out with the racemic acetate **2**. The 10:1 mixture of **2** and diformyl ester **3** was irradiated with a Hanovia 450-W lamp (Corex filter), and the progress of the reaction was followed by observing the change in the ultraviolet absorption maxima from 278 to 238 nm. Recovery of the excess acetate **2** by distillation and chromatography of the residue afforded a mixture of racemic photoproducts **5**, **18**, and **19** in 33% yield (Scheme III). No cyclobutane derivatives such as **4** were detected. The formation of racemic hemiacetal **5** as the major product (22% yield) indicated that the photoreaction was regioselective in the desired manner. This hemiacetal **5**[16] was identical with the hemiacetal prepared from the known racemic alcohol **20**.[19] Hemiacetal **5** afforded a 4:1 mixture of racemic alcohols **20** and **21** upon methanolysis. This mixture corresponded to the *ca.* 3:1 mixture of optically active alcohols **20** and **21** obtained by Battersby[2] in his degradation work on loganin (**1**). The minor photoproduct **19** yielded the known racemic alcohol **22**[19] on methanolysis.

Scheme III



The photochemical ring annelation of 1*S*,2*R* acetate **2** by methyl diformylacetate (**3**) was carried out as described above. The excess acetate was recovered by distillation and the residue was chromatographed to give a mixture of photoadducts. The major product **5**, $[\alpha]^{25}D$ +2.0°, was isolated by preparative tlc. A sample of optically active hemiacetal **5** afforded a 4:1 mixture of alcohols **20**, $[\alpha]^{25}D$ −45°, and **21**, $[\alpha]^{25}D$ +191°, upon methanolysis.

Until Büchi's synthesis of loganin (**1**)[16] almost no work on the conversion of iridoid aglucones into iridoid glucosides had been reported. Merz and Lehmann[33] attempted several variations of the Koenigs–Knorr reaction[34] on loganin aglucone but obtained only a small amount of an uncharacterized amorphous solid. In our laboratory many methods of coupling the glucose moiety to hemiacetal **5** were attempted. All variations of the Koenigs–Knorr reaction[34] resulted in complex mixtures with no loganin pentaacetate (**6**) being detected. However, a modification of the method of Kuhn and Wartburg[35] utilizing racemic or optically active hemiacetal **5** and 2,3,4,6-tetra-*O*-acetyl-β-D-glucose in the presence of boron trifluoride etherate gave a mixture of products containing loganin pentaacetate (**6**).[36] The addition of Drierite to this reaction mixture significantly improved the yield of loganin pentaacetate according to tlc. Using these conditions, optically active hemiacetal **5** was converted into loganin pentaacetate (**6**) in 17% yield after chromatography and recrystallization. The synthetic loganin pentaacetate (**6**), mp 139–140°, $[\alpha]^{25}D$ −79°, exhibited identical spectral properties and an undepressed mixture melting point with authentic loganin pentaacetate.[37] Loganin pentaacetate (**6**) previously had been converted into loganin (**1**) by Battersby and coworkers.[2]

Thus, a direct five-step synthesis of loganin pentaacetate (**6**) was carried out beginning with the prochiral reagent 5-methylcyclopentadiene (**7**). A high degree of asymmetry was induced during the formation of 1*R*,2*R* alcohol **8a** by asymmetric hydroboration. In this way a resolution step was avoided while optical asymmetry was introduced in the first step of the synthesis.

Experimental Section[38]

Racemic *trans*-2-Methyl-3-cyclopenten-1-ol (8). A solution of

(30) The ORD amplitude values for **12a** ($a = -63$) and **12b** ($a = +63$) are of the same order of magnitude as the amplitude value of $a_c = +23$ for (2*S*)-2-methylcyclopentanone (**12b**) calculated by Ouannes and Jacques on the basis of extensive molecular model studies; see C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 3611 (1965).

(31) A. C. Cope and D. L. Nealy, *J. Amer. Chem. Soc.*, **87**, 3122 (1965).

(32) *Cf.* G. A. Olah, G. Liang, and Y. K. Mo, *ibid.*, **94**, 3544 (1972), and references cited therein.

(33) K. W. Merz and H. Lehmann, *Arch. Pharm.*, **290**, 543 (1957).

(34) The Koenigs-Knorr reaction is the most general method of forming β-D-glucoside derivatives of alcohols; *cf.* W. L. Evans, D. D. Reynolds, and E. A. Talley, *Advan. Carbohyd. Chem.*, **6**, 27 (1951); J. Conchie, G. A. Levvy, and C. A. Marsh, *ibid.*, **12**, 157 (1957); W. W. Zorbach and K. V. Bhat, *ibid.*, 21, 273 (1966).

(35) M. Kuhn and A. von Wartburg, *Helv. Chim. Acta*, **51**, 1631 (1968); **52**, 948 (1969).

(36) This method of β-D-glucose formation was interesting since iridoid aglucones decompose in acid[17] and since 2,3,4,6-tetra-*O*-acetyl-β-D-glucose mutarotates to the more stable 2,3,4,6-tetra-*O*-acetyl-α-D-glucose in the presence of mild acids; *cf.* A. Georg, *ibid.*, **15**, 924 (1932).

(37) We are indebted to Professor A. I. Scott for a sample of loganin pentaacetate derived from natural sources.

(38) (a) A nitrogen atmosphere was maintained over all reaction mixtures. (b) The isolation procedure consisted of diluting the reaction

cyclopentadienylsodium was prepared according to King and Stone[39] from 71.0 g of sodium metal and 210.0 g of cyclopentadiene in 750 ml of tetrahydrofuran (THF). This solution was filtered through glass wool and added dropwise over a 9-hr period to a mixture of 639.0 g of methyl iodide and 300 ml of THF maintained at −78°. The cold mixture was stirred at −78° for 16 hr before 750 ml of 1.0 *M* borane in THF[40] was added dropwise over a 1-hr period. This mixture was stirred for 5 hr at −78° and for 16 hr at 0°.

Approximately one-half of the solution volume was removed under reduced pressure and was replaced with anhydrous ether. In this manner excess dienes were removed from the mixture. This solution was maintained at 0° as 225 ml of 3 *N* aqueous sodium hydroxide solution was slowly added, followed by the dropwise addition of 225 ml of 30% hydrogen peroxide. Solid sodium bisulfite was added to decolorize the dark solution and the mixture was saturated with solid sodium chloride. The product was isolated with ether and distilled at 65–75° (15 mm) to yield 77.2 g (35%) of a 9:1 mixture[41] of alcohols **8** and **9** contaminated by several impurities.

This material was further purified by the method of Hess and Brown.[42] The 77.2 g of oil was dissolved in 500 ml of ether and was extracted three times with 500-ml portions of 1 *M* aqueous silver nitrate solution. The combined aqueous layers were washed with ether. Excess sodium chloride was added to precipitate out silver chloride and the desired product was isolated with ether. Two careful distillations through a 6-in. Vigreux column afforded 45.0 g (20%) of pure alcohol **8**: bp 55–56° at 13 mm; ir (neat) 3400 (OH), 1070, and 710 cm^{-1}; nmr ($CDCl_3$) δ 5.66 (s, 2, –CH=), 4.02 (d of t, 1, $J_{1,7\alpha} = 7$ and $J_{1,3\beta} = J_{1,2} = 4$ Hz, H-1), and 1.05 (d, 3, $J = 7$ Hz, CH_3); 3,5-dinitrobenzoate derivative, mp 82–83°.

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.50; H, 10.19.

(1*R*,2*R*)-2-Methyl-3-cyclopenten-1-ol (8a). (A) By Asymmetric Hydroboration of Diene 7. A solution of cyclopentadienylsodium[39] was prepared from 18.8 g of sodium metal and 53.5 g of cyclopentadiene in 200 ml of tetrahydrofuran (THF). The solution was filtered and added dropwise to 171.0 g of methyl iodide in 150 ml of THF at −78° over a 5-hr period. Stirring was continued for an additional 16 hr at −78° to generate 5-methylcyclopentadiene (**7**).

During this time (+)-di-3-pinanylborane was prepared by adding 800 ml of 1.0 *M* borane in THF[40] to 240 g of (−)-α-pinene[43] to 0° and stirring the mixture for 16 hr at 0°. This suspension was cooled to −78° and the solution of 5-methylcyclopentadiene (**7**) was added. This heterogeneous mixture was stirred at −78° for 5 hr and at 0° for an additional 16 hr.

Approximately one-half of the solvent volume was removed under reduced pressure and replaced with dry ether. The mixture was maintained at 0° and 240 ml of 3 *N* sodium hydroxide solution was added, followed by the dropwise addition of 240 ml of 30% hydrogen peroxide. Solid sodium bisulfite was added to decolorize the dark solution and the mixture was saturated with sodium chloride. The product was isolated with ether and distilled at 59–81° (23 mm) affording 68.2 g of alcohol **8a** contaminated by diene dimers, (−)-α-pinene, and isopinocampheol. This oil was dissolved in 500 ml of ether and extracted three times with 1 *M* aqueous silver nitrate.[42] The aqueous layers were washed with ether and saturated with sodium chloride. The product was isolated with ether and distilled to give 26.5 g (33%) of colorless oil: bp 50–51° at 8 mm; $[\alpha]^{25}D$ −156° (*c* 1.05, CH_3OH). An analytical sample was isolated by preparative gas chromatography,[44] $[\alpha]^{25}D$ −169° (*c* 1.21, CH_3OH).

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.67; H, 10.18.

(B) By Saponification of Acid Phthalate 13a. A solution containing 3.63 g of 85% potassium hydroxide and 2.60 g of acid phthalate **13a** in 40 ml of water was stirred at 70° for 16 hr and cooled. The product was isolated with ether and distilled to yield 0.86 g (83%) of alcohol **8a**: bp 65–70° (bath temperature) at 10 mm; $[\alpha]^{25}D$ −175° (*c* 1.23, CH_3OH); ir ($CHCl_3$) 3620 (OH), 1060, 1020 cm^{-1}; nmr ($CDCl_3$) δ 5.66 (s, 2, –CH=), 4.02 (d of t, 1, $J_{1,7\alpha} = 7$ and $J_{1,3\beta} = J_{1,2} = 4$ Hz, H-1), and 1.05 (d, 3, $J = 7$ Hz, CH_3); 3,5-dinitrobenzoate derivative, mp 94–95°.

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.23; H, 10.24.

(1*S*,2*S*)-2-Methyl-3-cyclopenten-1-ol (8b). (A) By Asymmetric Hydroboration of Diene 7. 5-Methylcyclopentadiene (**7**), prepared from 18.8 g of sodium, 53.5 g of cyclopentadiene, and 171.0 g of methyl iodide in 350 ml of tetrahydrofuran (THF), was hydroborated with (−)-di-3-pinanylborane prepared from 800 ml of 1.0 *M* borane in THF[40] and 240 g of (+)-α-pinene.[45] Work-up utilizing the silver nitrate purification procedure of Hess and Brown[42] and distillation afforded 23.7 g (30%) of alcohol **8b**: bp 53–54° (10 mm); $[\alpha]^{25}D$ +155° (*c* 1.04, CH_3OH). An analytical sample was obtained by preparative gas chromatography:[44] $[\alpha]^{25}D$ +170° (*c* 1.23, CH_3OH).

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.68; H, 10.23.

(B) By Saponification of Acid Phthalate 13b. A solution of 3.20 g of 85% potassium hydroxide and 2.30 g of acid phthalate **13b** in 40 ml of water was stirred at 70° for 16 hr and cooled. The product was isolated with ether and distilled affording 0.78 g (85%) of alcohol **8b**: bp 65–70° (bath temperature) at 10 mm; $[\alpha]^{25}D$ +174° (*c* 1.03, CH_3OH); ir ($CHCl_3$) 3620 (OH), 1060, and 1020 cm^{-1}; nmr ($CDCl_3$) δ 5.66 (s, 2, –CH=), 4.02 (d of t, 1, $J_{1,7\alpha} = 7$ and $J_{1,3\beta} = J_{1,2} = 4$ Hz, H-1), and 1.05 (d, 3, $J = 7$ Hz, CH_3); 3,5-dinitrobenzoate derivative, mp 94–95°.

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.00.

Racemic *cis*-2-Methyl-3-cyclopenten-1-ol (9). A 3.52-g sample of racemic acetate **2** was added to 50 ml of 1 *N* methanolic potassium hydroxide and the mixture was stirred at room temperature for 18 hr. The product was isolated with ether and distilled affording 2.28 g (93%) of colorless oil: bp 50–55° at 15 mm; ir ($CHCl_3$) 3580 (OH), 1160, 1080 (sh), 1060, and 980 cm^{-1}; nmr ($CDCl_3$) δ 5.60 (s, 2, –CH=), 4.34 (m, 1, H-1), and 1.03 (d, 3, $J = 7$ Hz, CH_3).

This material was identical in all respects with the minor unsaturated alcohol isomer obtained by hydroboration-oxidation of diene **7** followed by preparative gas chromatography.[44]

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.53; H, 10.14.

(1*S*,2*R*)-2-Methyl-3-cyclopenten-1-ol (9). In the same manner, 2.98 g of optically active acetate **2** was saponified with 2.9 g of 85% potassium hydroxide in 25 ml of methanol to yield 1.91 g (92%) of a colorless oil: bp 43–45° at 7 mm; $[\alpha]^{25}D$ −106° (*c* 1.27, CH_3OH); ir ($CHCl_3$) 3620 (OH), 1160, 1080 (sh), 1060, and 980 cm^{-1}; nmr

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mixture with water, thoroughly extracting the mixture with the specified solvent, washing the combined extracts with water and saturated brine, and drying the extracts over anhydrous magnesium sulfate. Pyridine was removed from the organic phase by washing with 5% sulfuric acid. Acids were removed by washing with saturated aqueous sodium bicarbonate. The solvent was removed under reduced pressure after separation of the drying agent by filtration. (c) Melting points were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. Infrared spectra were obtained using a Beckmann IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was employed for ultraviolet absorption spectra. ORD and CD measurements were performed using a Jasco ORD/UV-5 spectropolarimeter with CD attachment. A Perkin-Elmer Model 141 polarimeter was employed for optical rotation measurements. Nuclear magnetic resonance spectra were determined with a Varian HA-100 spectrometer using tetramethylsilane as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV using a direct insertion probe. (d) Gas chromatography was carried out on Hewlett–Packard Model 402B and 5750 and Varian–Aerograph Model A-700 instruments. Helium was used as the carrier gas. Retention times are reported in minutes from the air peak. (e) Thin layer chromatography was carried out using Merck F_{254} silica gel plates. Thick layer chromatography plates made from Merck PF_{254} silica gel were used for preparative separations.

(39) R. B. King and F. G. A. Stone, *Inorg. Syn.*, 7, 99 (1963).

(40) This solution was purchased from the Ventron Corp. and was titrated according to H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **90**, 2915 (1968).

(41) The gas chromatogram showed peaks at 6.0 (3%, cyclopentanol), 7.1 (81%, **8**), 7.5 (9%, **9**), and 10.0 min (7%, cyclopentadiene dimers). A 20 ft × 0.25 in. stainless steel column of 5% Carbowax 20M on 100–120 mesh Chromosorb W was used at 150° with a helium flow of 60 cc/min.

(42) H. M. Hess and H. C. Brown, *J. Org. Chem.*, **32**, 4138 (1967).

(43) This material was obtained from the Chemical Samples Co., and was distilled over sodium metal: bp 155–156°; $[\alpha]^{25}D$ −47.5° (neat).

(44) A 10 ft × 0.5 in. stainless steel column of 20% SE-30 on 60–80 mesh Chromosorb W was used at 120° with a helium flow rate of 200 cc/min.

(45) This material was obtained from the Aldrich Chemical Co. and distilled over sodium metal at 155–156°. The rotation was $[\alpha]^{25}D$ +47.5° (neat).

($CDCl_3$) δ 5.60 (s, -CH=), 4.34 (m, 1, H-1), and 1.03 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.14; H, 10.33.

Racemic *trans*-2-Methylcyclopentan-1-ol (11). A 0.50-g sample of racemic alcohol **8** was hydrogenated at 1 atm over 20 mg of platinum oxide in 5 ml of acetic acid. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. Distillation gave 0.40 g (80%) of colorless mobile oil: bp 60–65° (bath temperature) at 10 mm; ir (neat) 3200 (OH), 1070, and 1010 cm^{-1}; nmr ($CDCl_3$) δ 3.73 (m, 1, H-1) and 1.00 (d, 3, J = 7 Hz, CH_3).

This material[46] was identical with the major alcohol formed by treatment of either 1-methylcyclopentene[23] or 2-methylcyclopentanone[24] with borane in tetrahydrofuran.

Anal. Calcd for $C_6H_{10}O$: C, 71.95; H, 12.08. Found: C, 72.23; H, 11.83.

(1*R*,2*R*)-2-Methylcyclopentan-1-ol (11a). A solution of 0.27 g of alcohol **8a** in 5 ml of methanol was hydrogenated at 1 atm over 50 mg of platinum oxide. The mixture was filtered, concentrated under reduced pressure, and distilled to yield 0.22 g (80%) of alcohol **11a**:[47] bp 65–70° (bath temperature) at 11 mm; $[\alpha]^{25}D$ −44.2° (*c* 1.00, CH_3OH); ir ($CHCl_3$) 3600 (OH) and 1060 cm^{-1}; nmr ($CDCl_3$) δ 3.73 (m, 1, H-1) and 1.00 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.81; H, 12.08.

(1*S*,2*S*)-2-Methylcyclopentan-1-ol (11b). (A) By Catalytic Hydrogenation of Alcohol 8b. In the above manner, 0.28 g of alcohol **8b** was hydrogenated at atmospheric pressure to give 0.23 g (81%) of alcohol **11b**: bp 70–75° (bath temperature) at 14 mm; $[\alpha]^{25}D$ +43.9° (*c* 1.00, CH_3OH); ir ($CHCl_3$) 3600 (OH) and 1060 cm^{-1}; nmr ($CDCl_3$) δ 3.73 (m, 1, H-1) and 1.00 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.93; H, 11.98.

(B) By Lithium Aluminum Hydride Reduction of Ketone 12b. A solution of 150 mg of ketone **12b** in 5 ml of ether was added dropwise to a suspension of 100 mg of lithium aluminum hydride in 10 ml of ether at 0°. After 1 hr, 0.20 ml of water and 0.16 ml of 10% aqueous sodium hydroxide were cautiously added. The mixture was stirred for 2 hr and filtered, and the filtrate was carefully concentrated under reduced pressure. The mixture of products was submitted to preparative gas chromatography[48] to yield 78 mg of the major alcohol **11b**: $[\alpha]D^{25}D$ +41.7° (*c* 1.36, CH_3OH); nmr ($CDCl_3$) δ 3.73 (m, 1, H-1) and 1.00 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_6H_{12}O$: 3, 71.95; H, 12.08. Found: C, 72.21; H, 11.83.

Racemic *cis*-2-Methylcyclopentan-1-ol. A solution of 0.10 g of racemic alcohol 9 in 2 ml of acetic acid was hydrogenated at 1 atm over 25 mg of platinum oxide. The mixture was filtered and the filtrate was distilled affording 0.09 g (90%) of mobile oil: bp 55–65° (bath temperature) at 12 mm; ir ($CHCl_3$) 3620 (OH), 1240, and 945 cm^{-1}; nmr ($CDCl_3$) δ 4.04 (m, 1, H-1) and 1.03 (d, 3, J = 7 Hz, CH_3).

This alcohol[46] was identical with the minor alcohol isomer from diborane reduction of 2-methylcyclopentanone and with the major alcohol isomer from disiamylborane reduction.[24]

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.00; H, 11.88.

(2*R*)-2-Methylcyclopentanone (12a). To a solution of 115 mg of alcohol **11a** in 1 ml of distilled acetone at 0° was added 0.30 ml of standard Jones reagent.[29] After hand swirling the solution for 2 min at 0°, isopropyl alcohol was added dropwise to destroy the excess oxidant. The reaction mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent yielded 102 mg (91%) of crude product which was fractionally distilled to yield a middle fraction of 34 mg of pure ketone **12a**: bp 60° (bath temperature) at 120 mm; $[\alpha]^{25}D$ −110.5° (*c* 1.19, CH_3OH); ir ($CHCl_3$) 1745 (CO), 1160, 1045, and 930 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (d, 3, J = 6 Hz, CH_3); ORD (*c* 0.069; dioxane): $[\phi]^{700}$ −74°, $[\phi]^{589}$ −116°, $[\phi]^{323}_{min}$ −3377°, $[\phi]^{315}_{max}$ −2489°, $[\phi]^{311}_{min}$ −2595°, $[\phi]^{301}$ 0°, $[\phi]^{277}_{max}$ +2951°, $[\phi]^{234}_{min}$ +1706°, $[\phi]^{210}$ +2489°; CD (*c* 0.010 *M*, dioxane): $[\theta]^{336}$ 0, $[\theta]^{317}$ −2643 (sh), $[\theta]^{306}_{min}$ −4786, $[\theta]^{301}_{max}$ −4500, $[\theta]^{297}_{min}$ −4643, $[\theta]^{240}$ 0.

After 24 hr in methanol, the rotation exhibited by ketone **12a** had fallen to $[\alpha]^{25}D$ −88°. Addition of a catalytic amount of sodium methoxide to this solution caused complete racemization to take place within seconds.

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.51; H, 10.20.

(2*S*)-2-Methylcyclopentanone (12b). In the same manner, 300 mg of alcohol **11b** was oxidized with standard Jones reagent[29] and distilled to yield 230 mg (78%) of a colorless oil, $[\alpha]^{25}D$ +109.5° (*c* 1.06, CH_3OH). This ketone **12b** was briefly reexposed to Jones reagent and distilled to yield 180 mg of a fragrant oil: bp 65–70° (bath temperature) at 150 mm; $[\alpha]^{25}D$ +110.1° (*c* 1.22, CH_3OH); $[\alpha]^{25}D$ +117.5° (*c* 1.01, $CHCl_3$); ir ($CHCl_3$) 1745 (CO), 1160, 1045, and 930 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (d, 3, J = 6 Hz, CH_3); ORD (*c* 0.070, dioxane): $[\phi]^{700}$ +62°, $[\phi]^{589}$ +112°, $[\phi]^{323}_{max}$ +3258°, $[\phi]^{316}_{min}$ +2347°, $[\phi]^{312}_{max}$ +2488°, $[\phi]^{302}$ 0°, $[\phi]^{280}_{min}$ −3013°, $[\phi]^{234}_{max}$ −1752°, $[\phi]^{210}$ −2453°; CD (*c* 0.007 *M*, dioxane): $[\theta]^{340}$ 0, $[\theta]^{318}$ +2286 (sh), $[\theta]^{306}_{max}$ +4214, $[\theta]^{302}_{min}$ +3929, $[\theta]^{298}_{max}$ +4143, $[\theta]^{240}$ 0.

A sample of this ketone was completely racemized by exposure to methanolic sodium methoxide in a few seconds.

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.10; H, 10.55.

(+)-α-Methylbenzylammonium Salt of Acid Phthalate 13a. To a solution of 7.5 g of racemic alcohol **8** in 40 ml of pyridine was added 11.3 g of phthalic anhydride and the solution was stirred at room temperature for 3 days. The mixture was poured into ice water and the product was isolated with ethyl acetate. Removal of the solvent gave 19.0 g (100%) of crude acid phthalate **13**: oil; ir ($CHCl_3$) 3300–2600 (acid OH), 1720 (CO, broad), 1300, 1135, and 1080 cm^{-1}.

A stirred solution of 19.0 g of racemic acid phthalate **13** in 40 ml of methanol was cooled to 0° and treated with 9.5 g of (+)-α-methylbenzylamine, $[\alpha]^{25}D$ +39° (neat). The solution was concentrated under reduced pressure to yield 28.5 g of off-white solid. This material was recrystallized seven times from acetone to yield 4.81 g (34%) of constant melting colorless needles: mp 155–156°; $[\alpha]^{25}D$ −70.9° (*c* 0.98, CH_3OH); ir ($CHCl_3$) 3300–2500 (NH_3), 1705 (CO), 1375, 1290, and 1260 cm^{-1}; nmr ($CDCl_3$) δ 8.80 (s, 3, NH_3), 7.48 (m, 9, aromatic), 5.57 (s, 2, -CH=), 4.94 (m, 1, -CH-O), 4.20 (m, 1, -CH-N), 1.46 (d, 3, J = 6 Hz, CH_3CH-N), and 0.96 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.00; H, 6.89; N, 3.76.

(−)-α-Methylbenzylammonium Salt of Acid Phthalate 13b. The first mother liquors from the resolution of the salt of **13a** (16.5 g) were dissolved in 70 ml of water and the solution was adjusted to pH 2 with 2 *N* sulfuric acid. The crude acid phthalate (10.9 g) was isolated with ethyl acetate. This material was dissolved in 30 ml of methanol at 0° and treated with 5.3 g of (−)-α-methylbenzylamine, $[\alpha]^{25}D$ −39° (neat). Removal of the solvent under reduced pressure yielded 16.2 g of yellow solid. Recrystallization to constant melting point and rotation gave 4.16 g (30%) of colorless needles: mp 155–156°; $[\alpha]^{25}D$ +71.0° (*c*, 0.97, CH_3OH); ir ($CHCl_3$) 3300–2500 (NH_3), 1705 (CO), 1375, 1290, and 1260 cm^{-1}; nmr ($CDCl_3$) δ 8.89 (s, 3, NH_3), 7.48 (m, 9, aromatic), 5.57 (s, 2, -CH=), 4.94 (m, 1, -CH-O), 4.20 (m, 1, -CH-N), 1.46 (d, 3, J = 6 Hz, CH_3CH-N), and 0.96 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.21; H, 7.02; N, 3.72.

(1*R*,2*R*)-2-Methyl-3-cyclopenten-1-ol Acid Phthalate (13a). The salt of **13a** (3.95 g) was dissolved in 50 ml of water and the solution was acidified to pH 2 with 2 *N* sulfuric acid solution. Isolation of the product with ethyl acetate afforded 2.65 g (100%) of a viscous oil: $[\alpha]^{25}D$ −91.9° (*c* 1.14, CH_3OH); ir ($CHCl_3$) 3300–2600 (acid OH), 1720 (CO, broad), 1300, 1135, and 1080 cm^{-1}; nmr ($CDCl_3$) δ 11.44 (s, 1, CO_2H), 7.68 (m, 4, aromatic), 5.65 (s, 2, -CH=), 5.22 (d of t, 1, $J_{1,5\alpha}$ = 7 and $J_{1,5\beta} = J_{1,2}$ = 4 Hz, H-1), and 1.15 ppm (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.23; H, 5.73. Found: C, 68.27; H, 5.72.

(1*S*,2*S*)-2-Methyl-3-cyclopenten-1-ol Acid Phthalate (13b). By the above method, 3.74 g of the corresponding salt was converted

(46) The SE-30 column[44] was used at 100° with a helium flow rate of 150 cc/min for this separation.

(47) Brown and coworkers calculated an optical rotation value of $[\alpha]^{25}D$ −28° for this substance based on a partially resolved sample; *cf.* H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 1071 (1964).

(48) The gas chromatogram showed peaks at 11.5 (19%, *cis*-2-methylcyclopentan-1-ol) and at 13.5 min (81%, alcohol **11b**). A 10 ft × 0.5 in. stainless steel column of 20% Carbowax 20M on 60–80 mesh Chromosorb W was used at 110° with a helium flow of 200 cc/min.

into 2.38 g (95%) of acid phthalate (**13b**): oil; $[\alpha]^{25}D$ +91.7° (*c* 1.16, CH_3OH); ir ($CHCl_3$) 3300–2600 (acid OH), 1720 (CO, broad), 1300, 1135, and 1080 cm^{-1}; nmr ($CDCl_3$) δ 11.32 (s, CO_2H), 7.68 (m, 4, aromatic), 5.65 (s, 2, -CH=), 5.22 (d of t, 1, $J_{1,5\alpha}$ = 7 and $J_{1,5\beta} = J_{1,2}$ = 4 Hz, H-1), and 1.15 (d, 3, *J* = 7 Hz, CH_3).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.23; H, 5.73. Found: C, 67.95; H, 5.75.

(1*R*,2*R*)-2-Methyl-3-cyclopenten-1-ol (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (14). (A) From Alcohol 8a Obtained by Resolution. A solution of 49 mg of alcohol **8a**, $[\alpha]^{25}D$ −175°, in 1 ml of pyridine was chilled in an ice bath, and 139 mg of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride,[26] $[\alpha]^{25}D$ +131° (*c* 1.10, CCl_4), was added dropwise by syringe. After 30 min the ice bath was removed and stirring was continued for 16 hr. Several chips of ice were added to decompose the excess acid chloride and the product was isolated with ethyl acetate. Distillation yielded 147 mg (94%) of a colorless oil: bp 130–135° (bath temperature) at 0.1 mm; $[\alpha]^{25}D$ −16.5° (*c* 1.06, $CHCl_3$); ir ($CHCl_3$) 1745 (CO), 1280, 1175, 1125, and 1025 cm^{-1}; nmr (CCl_4) δ 7.40 (m, 5, aromatic), 5.57 (s, 2, -CH=), 5.04 (d of t, $J_{1,5\alpha}$ = 7 and $J_{1,5\beta} = J_{1,2}$ = 4 Hz, H-1), 3.49 (s, 3, OCH_3), 2.83 (d of d, J_{vic} = 7 and J_{gem} = 17 Hz, H-5α), 2.82 (m, 1, H-2), 2.25 (d of d, 1, J_{vic} = 4 and J_{gem} = 17 Hz, H-5β), and 1.10 (d, 3, *J* = 7 Hz, CH_3). The nmr spectrum of the crude product indicated a maximum of 0.5% of diastereomeric ester **15**.[49]

Anal. Calcd for $C_{16}H_{17}F_3O_3$: C, 61.14; H, 5.45; F, 18.13. Found: C, 61.30; H, 5.36; F, 17.90.

(B) From Alcohol 8a Obtained by Asymmetric Hydroboration. A 49-mg sample of alcohol **8a**, $[\alpha]^{25}D$ −169°, was converted into 145 mg (93%) of ester **14**: bp 75–80° (bath temperature) at 0.01 mm; $[\alpha]^{25}D$ −13.3° (*c* 1.21, $CHCl_3$). The nmr spectrum showed that the crude product contained no more than 2.5% of the diastereomeric ester **15**.[49]

(1*S*,2*S*)-2-Methyl-3-cyclopenten-1-ol (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (15). (A) From Alcohol 8b Obtained by Resolution. In the above manner, 49 mg of alcohol **8b**, $[\alpha]^{25}D$ +174°, yielded 150 mg (95%) of a colorless oil: bp 130–135° (bath temperature) at 0.1 mm; $[\alpha]^{25}D$ +106° (*c* 1.21, $CHCl_3$); ir ($CHCl_3$) 1745 (CO), 1280, 1175, 1125, and 1025 cm^{-1}; nmr (CCl_4) δ 7.40 (m, 5, aromatic), 5.57 (s, 2, -CH=), 5.06 (d of t, 1, $J_{1,5\alpha}$ = 7 and $J_{1,5\beta} = J_{1,2}$ = 4 Hz, H-1), 3.49 (s, 3, OCH_3), 2.88 (d of d, 1, J_{vic} = 7 and J_{gem} = 17 Hz, H-5α), 2.72 (d of q, 1, $J_{2,1}$ = 4 and $J_{2,6}$ = 7 Hz, H-2), 2.37 (d of d, 1, J_{vic} = 4 and J_{gem} = 17 Hz, H-5β), and 1.06 (d, 3, *J* = 7 Hz, CH_3). The nmr spectrum of the crude product showed a maximum of 1% of diastereomeric ester **14**.[49]

Anal. Calcd for $C_{16}H_{17}F_3O_3$: C, 61.14; H, 5.45; F, 18.13. Found: C, 60.87; H, 5.47; F, 18.06.

(B) From Alcohol 8b Obtained by Asymmetric Hydroboration. A 49-mg sample of alcohol **8b**, $[\alpha]^{25}D$ +170°, was converted into 148 mg (94%) of an oil: bp 75–80° (bath temperature) at 0.01 mm; $[\alpha]^{25}D$ +105° (*c* 1.16, $CHCl_3$). The 100-MHz nmr spectrum of the crude product indicated the presence of no more than 2% of ester **14**.[49]

Preparation of Mixtures of Esters 14 and 15. (A) From Racemic Alcohol 8. A stirred solution of 49 mg of racemic alcohol **8** in 1 ml of dry pyridine was cooled to 0° and 139 mg of acid chloride was added dropwise. After 16 hr at room temperature the mixture was poured onto crushed ice and the product was isolated with ethyl acetate affording 150 mg (95%) of a mixture of esters **14** and **15**: bp 130–135° (bath temperature) at 0.1 mm; $[\alpha]^{25}D$ +45.4° (*c* 1.09, $CHCl_3$). The nmr spectrum of the crude product indicated a 50:50 mixture of esters **14** and **15**.[49]

(B) From Partially Resolved Alcohol 8b. In the above manner 49 mg of a 10:90 mixture of **8a** and **8b**, $[\alpha]^{25}D$ +139°, was transformed into 150 mg (95%) of a mixture of esters **14** and **15**: bp 130–135° (bath temperature) at 0.1 mm; $[\alpha]^{25}D$ +91.0° (*c* 1.27, $CHCl_3$). The 100-MHz nmr spectrum of the crude product showed a 11:89 mixture of esters **14** and **15**.[49]

(1*R*,2*R*)-2-Methyl-3-cyclopenten-1-ol Benzoate (16a). A stirred solution of 98 mg of alcohol **8a** in 3 ml of pyridine was cooled to 0° and 168 mg of benzoyl chloride was carefully added. After 1 hr at 0° and 16 hr at room temperature the mixture was poured into ice water. The product was isolated with ether affording 185 mg (91%) of colorless oil: bp 70–75° (bath temperature) at 0.02 mm; $[\alpha]^{25}D$ −125° (*c* 1.41, CH_3OH); ir ($CHCl_3$) 1710 (CO), 1290, 1120, 1070, and 1030 cm^{-1}; nmr ($CDCl_3$) δ 7.72 (m, 5, aromatic), 5.68 (s, 2, -CH=), 5.15 (d of t, 1, $J_{1,5\alpha}$ = 7 and $J_{1,5\beta} = J_{1,2}$ = 4 Hz, H-1), and 1.15 (d, 3, *J* = 7 Hz, CH_3): ORD (*c* 0.255, dioxane): $[\phi]^{700}$ −155°, $[\phi]^{589}$ −228°, $[\phi]^{238}_{min}$ −8321°, $[\phi]^{224}_{max}$ −5151°, $[\phi]^{208}$ −11,689°; CD (*c* 0.0127 *M*, dioxane): $[\theta]^{310}$ 0, $[\theta]^{227}_{min}$ −6667, $[\theta]^{215}_{max}$ −2540, $[\theta]^{210}$ −4921.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.24; H, 7.07.

(1*S*,2*S*)-2-Methyl-3-cyclopenten-1-ol Benzoate (16b). In the same manner, 98 mg of alcohol **8b** was converted into 190 mg (94%) of benzoate **16b**: bp 70–75° (bath temperature) at 0.02 mm; $[\alpha]^{25}D$ +124° (*c* 1.32, CH_3OH); ir ($CHCl_3$) 1710 (CO), 1290, 1120, 1070, and 1030 cm^{-1}; nmr ($CDCl_3$) δ 7.72 (m, 5, aromatic), 5.68 (s, 2, -CH=), 5.15 (d of t, 1, $J_{1,5\alpha}$ = 7 and $J_{1,5\beta} = J_{1,2}$ = 4 Hz, H-1), and 1.15 (d, 3, *J* = 7 Hz, CH_3); ORD (*c* 0.255, dioxane): $[\phi]^{700}$ +216, $[\phi]^{589}$ +186°, $[\phi]^{238}_{max}$ +7523°, $[\phi]^{225}_{min}$ +4553°, $[\phi]^{206}$ +10,888°; CD (*c* 0.0064 *M*, dioxane): $[\theta]^{330}$ 0, $[\theta]^{229}_{max}$ +6032, $[\theta]^{212}_{min}$ +3333, $[\theta]^{210}$ +4444.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.47; H, 7.15.

(1*R*,2*R*)-2-Methylcyclopentan-1-ol Benzoate (17a). In the above manner, 60 mg of alcohol **11a** in 2 ml of pyridine was converted into 114 mg (93%) of colorless oil: bp 70–75° (bath temperature) at 0.2 mm; $[\alpha]^{25}D$ −59.8° (*c* 1.22, CH_3OH); ir ($CHCl_3$) 1710 (CO), 1320, 1280, 1120, 1070, and 1030 cm^{-1}; nmr ($CDCl_3$) δ 7.72 (m, 5, aromatic), 4.89 (m, 1, H-1), and 1.03 (d, 3, *J* = 7 Hz, CH_3); ORD (*c* 0.238, dioxane): $[\phi]^{700}$ −82°, $(\phi)^{589}$ −95°, $[\phi]^{239}_{min}$ −3218°, $[\alpha]^{220}_{max}$ −858°, $[\alpha]^{210}$ −1502°; CD (*c* 0.0119 *M*, dioxane): θ^{310} 0, $[\theta]^{256}_{max}$ +155, $[\theta]^{246}$ 0, $[\theta]^{228}_{min}$ −2749, $[\theta]^{210}$ 0.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.68; H, 8.19.

(1*S*,2*S*)-2-Methylcyclopentan-1-ol Benzoate (17b). By the same procedure, 61 mg of alcohol **11b** was transformed into 112 mg (92%) of benzoate **17b**: bp 70–75° (bath temperature) at 0.2 mm; $[\alpha]^{25}D$ +59.6° (*c* 1.46, CH_3OH); ir ($CHCl_3$) 1710 (CO), 1320, 1280, 1120, 1070, and 1030 cm^{-1}; nmr ($CDCl_3$) δ 7.72 (m, 5, aromatic), 4.89 (m, 1, H-1), and 1.03 (d, 3, *J* = 7 Hz, CH_3); ORD (*c* 0.328; dioxane): $[\phi]^{700}$ +72°, $[\phi]^{589}$ +108°, $[\phi]^{235}_{max}$ +2803°, $[\phi]^{220}_{min}$ 0°; CD (*c*, 0.0164 *M*, dioxane): $[\theta]^{300}$ 0, $[\theta]^{253}_{min}$ −206, $[\theta]^{242}$ 0, $[\phi]^{228}_{max}$ +2750, $[\theta]^{210}$ 750.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.19; H, 7.98.

Racemic *cis*-2-Methyl-3-cyclopenten-1-ol Acetate (2). A stirred solution of 35.0 g of alcohol **8** in 150 ml of pyridine was cooled to 0° and 45.0 g of methanesulfonyl chloride was added dropwise. After 2 hr at 0°, the mixture was poured onto crushed ice and the product was isolated with ether affording 63.0 g (100%) of unstable racemic mesylate **10**: oil; ir (neat) 1340 (SO_2) and 1170 (SO_2), 940, 890, and 860 cm^{-1}; nmr ($CDCl_3$) δ 5.65 (s, 2, -CH=), 4.90 (d of t, 1, $J_{1,5\alpha}$ = 7 and $J_{1,5\beta} = J_{1,2}$ = 4 Hz, H-1), 3.00 (s, 3, SO_2CH_3), and 1.12 (d, 3, *J* = 7 Hz, CH_3).

A 62.0-g sample of this material was immediately dissolved in 500 ml of 1:1 hexamethylphosphoramide–acetone and 133.0 g of anhydrous tetraethylammonium acetate[31] was quickly added. The mixture was stirred at 60–65° for 2 days and cooled. The mixture was poured into ice water and the product was isolated with pentane. Removal of solvent under reduced pressure (bath temperature 25°) afforded 43.4 g of crude product which contained traces of mesylate **10**. The oil was distilled through a short column at 22–23° (0.15 mm) into a receiver cooled to −78°. This distillate was redistilled through a 6-in. Vigreux column yielding 31.0 g (63%) of racemic acetate **2**: bp 45–46° at 8 mm; ir ($CHCl_3$) 1735 (CO), 1270, 1180, 1055, and 1025 cm^{-1}; nmr ($CDCl_3$) δ 5.65 (s, 2, -CH=), 5.36 (d of t, 1, $J_{1,5\beta} = J_{1,2}$ = 6.5 and $J_{1,5\alpha}$ = 4 Hz, H-1), 2.04 (s, 3, CH_3CO), and 0.97 (d, 3, *J* = 7 Hz, CH_3).

This cis acetate **2** (t_R' 6.4 min) was readily distinguishable from the corresponding trans acetate (t_R' 7.8 min), prepared from alcohol **8**, using the 0.25-in. Carbowax column[41] at 110° with a flow rate of 67 cc/min.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.45; H, 8.88.

(1*S*,2*R*)-2-Methyl-3-cyclopenten-1-ol Acetate (2). In the above manner, a 26.5-g sample of alcohol **8a** in 100 of pyridine at 0° was treated with 34.3 g of methanesulfonyl chloride. After 2 hr, the mixture was poured onto ice and the product was isolated with ether to give 48.0 g (100%) of optically active mesylate **10**: oil; $[\alpha]^{25}D$ −99.3° (*c* 1.15, CH_3OH); ir (neat) 1340 (SO_2), 1170 (SO_2),

(49) The 50–150-Hz region of each 100-MHz nmr spectrum was isolated and expanded (100-Hz sweep width). The percentages of diastereomeric esters **14** and **15** were calculated on the basis of the C-2 methyl peak heights and areas. These esters did not exhibit differences in their respective ^{19}F nmr spectra (54.6 MHz) and could not be separated by gas chromatography using a variety of columns and conditions.

940, 890, and 860 cm^{-1}; nmr ($CDCl_3$) δ 5.65 (s, 2, -CH=), 4.90 (d of t, 1, $J_{1,5\alpha} = 7$ and $J_{1,5\beta} = J_{1,2} = 4$ Hz, H-1), 3.00 (s, 3, SO_2CH_3), and 1.12 (d, 3, $J = 7$ Hz, CH_3).

A mixture of 48.0 g of crude mesylate **10**, 106.0 g of purified tetraethylammonium acetate,[50] 250 ml of hexamethylphosphoramide, and 250 ml of acetone was stirred at 60–65° for 24 hr. The dark mixture was poured into ice water and the product was isolated with pentane. The crude product was distilled at 22–23° (0.15 mm) into a receiver cooled to −78° to afford 30.2 g of yellow oil. This material was fractionated at 45–46° (8 mm) through a 6-in. Vigreux column to yield 23.0 g (61%) of optically active acetate **2**: $[\alpha]^{25}D$ −94° (*c* 1.08, CH_3OH). The analytical sample was secured *via* preparative gas chromatography:[46] $[\alpha]^{25}D$ −100° (*c* 1.20, CH_3OH); ir ($CHCl_3$) 1735 (CO), 1270, 1180, 1055, and 1025 cm^{-1}; nmr ($CDCl_3$) δ 5.65 (s, 2, -CH=), 5.36 (d of t, 1, $J_{1,5\beta} = J_{1,2} = 6.5$ and $J_{1,5\alpha} = 4$ Hz, H-1), 2.04 (s, 3, CH_3CO), and 0.97 (d, 3, $J = 7$ Hz, CH_3).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.60; H, 8.61.

Racemic Loganin Aglucone 6-Acetate (5). (A) From Photolysis of Racemic Acetate 2 and Diformyl Ester 3. A mixture of 37.0 g of acetate **2** and 3.43 g of methyl diformylacetate (**3**)[16] was photolyzed[51] for 44 hr. During this time the 278 nm maximum was replaced by a 238 nm maximum in the ultraviolet spectrum.

The excess acetate **2** (28.0 g) was removed by distillation at 53–57° (13 mm) using a short distilling column. The distillation residue (9.5 g) was chromatographed on Merck 0.05-0.20 mm silica gel. Elution with 15% ethyl acetate in benzene afforded 2.33 g (33%) of a mixture of racemic photoproducts **5**, **18**, and **19**. The mixture was further purified by thick layer chromatography (3:1 benzene–ethyl acetate) to yield 1.54 g (22%) of racemic hemiacetal **5**: light green oil; ir ($CHCl_3$) 3610 (OH), 1735 (CO), 1710 (CO), 1640 (C=C), 1290, 1260, and 1110 cm^{-1}; uv (C_2H_5OH) 236 nm (ϵ 10,050); nmr ($CDCl_3$) δ 7.38 (d, 1, $J = 1$ Hz, —CH=), 5.18 (m, 1, H-6), 4.98 (m, 1, H-1), 3.68 (s, 3, OCH_3), 3.06 (m, 1, H-4a), 2.04 (s, 3, CH_3CO), and 1.03 (d, 3, $J = 7$ Hz, CH_3); mass spectrum *m/e* (rel intensity) 270 (M^+, 10), 239 (9), 210 (33), 192 (20), 182 (45), 178 (35), 160 (35), 150 (100), 149 (65).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.78; H, 6.71. Found: C, 57.73; H, 6.72.

(B) From Racemic Acetal 20. A mixture of 50 mg of alcohol **20**,[19] 0.1 ml of acetic anhydride, and 2 ml of pyridine was stirred overnight at room temperature. Work-up afforded 55 mg of the crude acetate derivative: ir ($CHCl_3$) 1730 (CO), 1710 (CO), 1640 (C=C), 1290, 1260, 1185, and 1080 cm^{-1}. This material was dissolved in 3 ml of 1:1 acetic acid–water containing 3 drops of 70% perchloric acid. The solution was stirred at 80° for 1.5 hr and cooled. The product mixture was isolated with ethyl acetate and purified by thick layer chromatography (1:1 benzene-ethyl acetate) to yield 27 mg (52%) of a pale green oil: ir ($CHCl_3$) 3620 (OH), 1735 (CO), 1710 (CO), 1640 (C=C), 1290, 1260, and 1110 cm^{-1}; uv (C_2H_5OH) 236 nm (ϵ 9,500); nmr ($CDCl_3$) δ 7.38 (d, 1, $J = 1$ Hz, -CH=), 5.18 (m, 1, H-6), 5.00 (m, 1, H-1), 3.68 (s, 3, OCH_3), 3.06 (m, 1, H-4a), 2.04 (s, 3, CH_3CO), and 1.03 (d, 3, $J = 7$ Hz, CH_3).

Loganin Aglucone 6-Acetate (5). In the above manner a 10:1 mixture of optically active acetate **2** and methyl diformylacetate (**3**) was photolyzed to yield a mixture of optically active products **5**, **18**, and **19**. Preparative thick layer chromatography afforded the loganin aglucone derivative **5** (20%): oil; $[\alpha]^{25}D$ +2.0° (*c* 1.17, $CHCl_3$); ir ($CHCl_3$) 3620 (OH), 1735 (CO), 1710 (CO), 1640 (C=C), 1290, 1260, and 1110 cm^{-1}; uv max (C_2H_5OH) 236 nm (ϵ 10,530); nmr ($CDCl_3$) δ 7.38 (d, 1, $J = 1$ Hz, —CH=), 5.18 (m, 1, H-6), 4.98 (m, 1, H-1), 3.68 (s, 3, OCH_3), 3.06 (m, 1, H-4a), 2.04 (s, 3, CH_3CO), and 1.03 (d, 3, $J = 7$ Hz, CH_3).

Racemic Loganin Aglucone *O*-Methyl Ethers (20 and 21). A 274-mg sample of purified racemic aglucone **5** and 10 mg of *p*-toluenesulfonic acid monohydrate was stirred in 100 ml of methanol for 16 hr at room temperature. Sodium methoxide (108 mg) was added and the solution was stirred for 4 additional hr. The mixture was neutralized with acetic acid and the product was isolated with ether and fractionated by preparative thick layer chromatography (1:1 benzene–ethyl acetate). From 221 mg of crude mixture was obtained 133 mg (54%) of the more polar component identified as alcohol **20**:[19] oil; bp 130–135° (bath temperature) at 0.05 mm; ir ($CHCl_3$) 3620 (OH), 1705 (CO), 1640 (C=C), 1295, 1180, and 1080 cm^{-1}; uv max (C_2H_5OH) 238 nm (ϵ 12,000); nmr ($CDCl_3$) δ 7.38 (d, 1, $J = 1$ Hz, —CH=), 4.62 (d, 1, $J = 4$ Hz, H-1), 4.09 (t, 1, $J = 5$ Hz, H-6), 3.69 (s, 3, CO_2CH_3), 3.48 (s, 3, OCH_3), 3.12 (m, 1, H-4a), and 1.10 (d, 3, $J = 7$ Hz, CH_3); mass spectrum *m/e* (rel intensity) 242 (M^+, 9), 224 (10), 211 (7), 210 (8), 178 (7), 160 (5), 139 (12), 85 (100).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.65; H, 7.42.

A less polar component (33 mg, 14%) was identified as alcohol **21**: oil; ir ($CHCl_3$) 3620 (OH), 1705 (CO), 1640 (C=C), 1300, 1160, 1090, and 1080 cm^{-1}; uv max (C_2H_5OH) 238 nm (ϵ 8950); nmr ($CDCl_3$) δ 7.40 (d, 1, $J = 1$ Hz, —CH=), 4.90 (d, 1, $J = 3$ Hz, H-1), 4.17 (m, 1, H-6), 3.69 (s, 3, CO_2CH_3), 3.42 (s, 3, OCH_3), 3.10 (m, 1, H-4a), and 1.14 (d, 3, $J = 7$ Hz, CH_3); mass spectrum *m/e* (rel intensity) 242 (M^+, 3), 224 (3), 211 (3), 210 (4), 192 (6), 178 (4), 139 (8), 85 (100). Additionally, 23 mg (9%) of a 1:1 mixture of unknown aglucone *O*-methyl ethers was isolated. Integration of the H-1 acetal protons in the 100-MHz nmr spectrum of the crude product indicated a 4:1 mixture of alcohols **20** and **21**.

Loganin Aglucone *O*-Methyl Ethers (20 and 21).[2] In the same manner, 61 mg of aglucone **5** was converted into 45 mg in a 4:1 mixture of alcohol **20** {oil; $[\alpha]^{25}D$ −45° (*c* 1.16, $CHCl_3$); nmr ($CDCl_3$) δ 7.38 (d, 1, $J = 1$ Hz, —CH=), 4.62 (d, 1, $J = 4$ Hz, H-1), 4.09 (t, 1, $J = 5$ Hz, H-6), 3.69 (s, 3, CO_2CH_3), 3.48 (s, 3, OCH_3), 3.12 (m, 1, H-4a), and 1.10 (d, 3, $J = 7$ Hz, CH_3)} and alcohol **21** {oil; $[\alpha]^{25}D$ +191° (*c* 0.92, $CHCl_3$); nmr ($CDCl_3$) δ 7.40 (d, 1, $J = 1$ Hz, —CH=), 4.90 (d, 1, $J = 3$ Hz, H-1), 4.17 (m, 1, H-6), 3.69 (s, 3, CO_2CH_3), 3.42 (s, 3, OCH_3), 3.10 (m, 1, H-4a), and 1.14 (d, 3, $J = 7$ Hz, CH_3)} which were separated by preparative thick layer chromatography. In addition, 9 mg of a mixture of unknown aglucone *O*-methyl ethers, $[\alpha]^{25}D$ −1.3° (*c* 0.87, $CHCl_3$), was obtained.

Racemic Alcohol 22. A 167-mg sample of photoproducts **18** and **19** was submitted to methanolysis to yield 121 mg of a mixture of products. Purification by thick layer chromatography (1:1 benzene–ethyl acetate) gave 32 mg of alcohol **22**:[19] mp 89–90°; ir ($CHCl_3$) 3620 (OH), 1705 (CO), 1640 (C=C), 1190, and 1110 cm^{-1}; uv max (C_2H_5OH) 240 nm (ϵ 11,380); nmr ($CDCl_3$) δ 7.46 (s, 1, —CH=), 5.06 (d, 1, $J = 8$ Hz, H-1), 4.20 (m, 1, H-6), 3.69 (s, 3, CO_2CH_3), 3.52 (s, 3, OCH_3), and 1.13 (d, 3, $J = 7$ Hz, CH_3); mass spectrum *m/e* (rel intensity) 242 (M^+, 7), 224 (2), 211 (2), 210 (7), 192 (7), 178 (5), 139 (6), 128 (15), 85 (100).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.58; H, 7.43.

Loganin Pentaacetate (6). (A) From Racemic Hemiacetal 5. This procedure was based on the method of Kuhn and Wartburg.[45] A mixture of 135 mg of racemic aglucone **5**, 524 mg of 2,3,4,6-tetra-*O*-acetyl-β-D-glucose,[52] and 400 mg of anhydrous calcium sulfate (Drierite) in 3 ml of 1,2-dichloroethane was chilled in an ice bath and 0.12 ml of boron trifluoride etherate was added dropwise by syringe. After 1 hr the cooling bath was removed and the mixture was stirred at room temperature for 24 hr. The dark solution was neutralized with pyridine in 1,2-dichloroethane. The mixture was poured into water and the product was isolated with ethyl acetate. This material was fractionated by thick layer chromatography (2:1 ether–petroleum ether) to yield 68 mg of uv-active material. This mixture of glucosides was further purified by tlc (5:1 benzene-ether) to afford 14 mg of an oil. This material was dissolved in 0.5 ml of ethanol and seeded with 0.1 mg of authentic loganin pentaacetate[37] to yield 5.6 mg (3.6% yield) of white crystals, mp 132–136°. The mass spectrum and 100-MHz nmr spectrum were identical with authentic loganin pentaacetate. An additional recrystallization yielded fine white clusters of needles melting at 136–138° which exhibited no melting point depression when mixed with authentic loganin pentaacetate.

(50) During the course of this work anhydrous tetraethylammonium acetate (Eastman Kodak) no longer became available. Tetraethylammonium acetate tetrahydrate (Eastman Kodak) was azeotropically distilled with benzene over a 5-day period to remove the water of hydration. This anhydrous material was further purified by the method of J. Steigman and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 2536 (1937). Lower yields of acetate **2** were obtained with some batches of tetraethylammonium acetate purified in this manner.

(51) A Hanovia 450-W mercury lamp (679 A-36) was used in a water-jacketed Vycor immersion well with a Corex (Corning 9700) filter sleeve. Stirring was effected by a stream of nitrogen introduced through a gas dispersion tube fitted in the bottom of the reaction vessel. The photoapparatus was partially immersed in a water bath to keep the reaction mixture near room temperature.

(52) This glucose derivative, mp 136–137°, $[\alpha]^{25}D$ +14.8 (*c* 1.02, $CHCl_3$), was prepared by the procedure of C. M. McCloskey and G. H. Coleman, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, pp 434–436.

(B) From Loganin Aglucone 6-Acetate (5). To an ice-cold solution of 105 mg of optically active aglucone **5**, 408 mg of 2,3,4,6-tetra-*O*-acetyl-β-D-glucose,[52] and 500 mg of Drierite in 3 ml of 1,2-dichloroethane was added dropwise 0.10 ml of boron trifluoride etherate. The mixture was stirred at 0° for 2 hr and at room temperature for 36 hr. After neutralization with pyridine, the mixture was poured into water and the product (550 mg) was isolated with ethyl acetate. The viscous oil was fractionated by thick layer chromatography to give 165 mg of a glucoside mixture. Further purification by tlc yielded 50 mg of an oil, $[\alpha]^{25}D$ −60° (*c* 1.05, $CHCl_3$), which crystallized on standing. The solid was recrystallized twice from ethanol to give 40 mg (17%) of fine white needles: mp 139–140° (lit.[2] mp 140–141°); $[\alpha]^{25}D$ −79.1° (*c* 0.35, $CHCl_3$) {lit.[2] $[\alpha]^{22}D$ −79.6° (*c* 0.39, $CHCl_3$)}; ir ($CHCl_3$) 1740 (CO, broad), 1710 (CO), 1645 (C=C), 1255, 1085, 1070, and 1045 cm^{-1}; uv (C_2H_5OH) 233 nm (ε 10,600); nmr ($CDCl_3$) δ 7.31 (s, 1, —CH=), 3.70 (s, 3, OCH_3), 3.02 (m, 1, H-4a), 2.09 (s, 3, CH_3CO), 2.03 (s, 6, CH_3CO), 2.00 (s, 3, CH_3CO), 1.81 (s, 3, CH_3CO), and 1.02 (d, 3, J = 7 Hz, CH_3); mass spectrum *m/e* (rel intensity) 600 (M^+, 0.1), 5.69 (0.1), 540 (0.3), 331 (70), 271 (5), 253 (4), 193 (35), 169 (100), 109 (40). A 1:1 mixture of this material and authentic loganin pentaacetate exhibited mmp 139–140°.

Anal. Calcd for $C_{27}H_{36}O_{15}$: C, 54.00; H, 6.04. Found: C, 53.90; H, 6.00.

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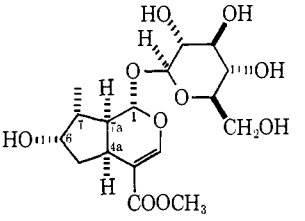
Total Synthesis of Loganin

G. Büchi,* John A. Carlson,[1] J. E. Powell, Jr.,[2] and L.-F. Tietze

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received July 27, 1972*

Abstract: A synthesis of loganin, a monoterpene glucoside occupying a central position in the biosynthesis of secoiridoids and alkaloids, is described. The photochemical cycloaddition of 2-formylmalonaldehydic acid methyl ester to the tetrahydropyranyl ether of 3-cyclopentenol is the key step in the synthesis, allowing the construction of the tetrahydrocoumalate unit typical of iridoids in a single operation. Methanolysis followed by oxidation with chromium trioxide afforded the crystalline ketoacetal **7**. The methyl group was introduced regioselectively *via* the *n*-butylthiomethylene ketone and the resulting product **12** epimerized to the more stable epimer **13**. Reduction of the carbonyl group and treatment of the corresponding mesylate with tetraethylammonium acetate followed by hydrolysis with aqueous acetic acid–perchloric acid gave loganol 5-acetate (**21**). Glucosidation of racemic **21** using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**23**) yielded optically active loganin pentaacetate which had previously been converted to loganin.

The glucoside loganin, first isolated from *Strychnos nux vomica*,[3] is a widely distributed product of secondary plant metabolism[4] and a key intermediate in the biosynthesis of *Corynanthe*, *Aspidosperma*, *Iboga*, *Ipecacuanha*, and structurally simpler monoterpene alkaloids.[5] Its detailed structure was established by chemical means[6–8] and confirmed by X-ray analysis of the methoxybromide.[9] In this paper we present details on the total synthesis of loganin (**1**),[10] which represents the first synthesis of an iridoid glucoside.[11]



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Our synthetic plan called for photochemical addition of 2-formylmalonaldehydic acid methyl ester (**3**) to a symmetrical cyclopentene[12] already containing the secondary hydroxyl group of loganin (**1**), followed by introduction of the *C*-methyl group and glucosidation. 2-Formylmalonaldehydic acid methyl ester (**3**) was formed after aqueous work-up when methyl 3,3-dimethoxypropionate, available from the condensation of ketene with trimethyl orthoformate,[13] was acylated with methyl formate in the presence of sodium.[14] Photochemical cycloaddition of the tricarbonyl compound **3** to 3-cyclopentenol[15,16] led to a multitude of products. Irradiation of a mixture of **3** and the tetrahydropyranyl

(1) National Institutes of Health Predoctoral Fellow 1966–1969.
(2) National Institutes of Health Predoctoral Fellow 1967–1969.
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