for the corresponding reaction of chloroacetaldehyde. The carbonyl group does not interact directly with the attacking nucleophile.

(E) The S_N2 reaction of the chloride ion with allyl chloride is predicted to take place without activation in the gas phase, by addition of chloride ion to the CC double bond to form a species superficially resembling the 1,3-dichloro-2-propyl anion. It contains a delocalized six-electron system, isoconjugate with the π system in pentadienyl anion and derived from the allyl cation by interaction of its terminal 2p AOs with the two chloride ions. The anti isomer is the more stable. S_N2' reactions of anionic nucleophiles in solution are slower than their S_N2 counterparts because of the greater energy needed to form the intermediate complex. Syn S_N2' attack by primary or secondary amines is attributed to hydrogen bonding between the entering and leaving groups. Preliminary studies indicate that the S_N2' reaction may be favored in a poor solvent for anions if ion pairing is repressed by use of a large cation.

(F) Since the bonding in hypervalent compounds is now commonly attributed to three-center four-electron bonds which are entirely analogous to that in an S_N2 TS, it seems surprising that the latter should be a saddle point, rather than a minimum, on the potential surface. This problem is made even more acute by the calculations reported here, which indicate this to be the case for S_N2' reactions. The difference seems to be due to the small size of the carbon atom. This leads to excessive steric repulsions when five other groups are attached. The failure of nitrogen or oxygen to form hypervalent compounds can be explained in the same way, the steric requirements of a lone pair of electrons being by no means negligible.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research (Contract F49620-83-C-0024) and the Robert A. Welch Foundation (Grant F-126). The calculations were carried out in part with a Digital VAX 11/780 computer, provided by grants from the National Science Foundation and The University of Texas at Austin, and in part with the CDC 6600 and Dual Cyber 170/150 computers at The University of Texas Computation Center.

Registry No. 5a, 100-44-7; **5b**, 352-11-4; **5c**, 35421-08-0; **5d**, 824-94-2; **5e**, 65581-19-3; **5f**, 100-14-1; **7**, 107-20-0; **12**, 107-05-1; CH_3Cl, 74-87-3; CH_3CH_2Cl, 75-00-3; $(CH_3)_2CHCl$, 75-29-6; $(CH_3)_3CCl$, 507-20-0; $(CH_3)_3CCH_2Cl$, 753-89-9; CH_2Cl_2, 75-09-2; $CHCl_3$, 67-66-3; CCl_4, 56-23-5.

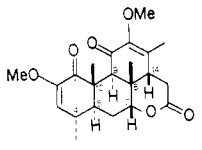
Quassinoids: Total Synthesis of *dl*-Quassin

Giovanni Vidari,[1] Sergio Ferriño, and Paul A. Grieco*

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47405. *Received November 21, 1983*

Abstract: The total synthesis of quassin (**1**), the major constituent of quassia wood, is described in racemic form. The synthesis features the Lewis acid catalyzed intermolecular Diels–Alder reaction between dienophile **8** and ethyl (*E*)-4-methyl-3,5-hexadienoate (**9**). Diels–Alder adduct **10** is transformed in straightforward fashion into tetracyclic diketone **15**, which is elaborated via a two-step sequence into neoquassin in β-*O*-methyl ether **49** (R = Me). Selective hydrolysis of **49** (R = Me) and subsequent oxidation provides *dl*-quassin.

The existence of bitter principles in quassia wood (*Quassia amara*) was first reported[2] in the literature in 1835; however, early attempts to isolate and purify the chemical constituents were unsuccessful. It was not until 1937, a century later, that Clark[3] succeeded in isolating and partially purifying quassin (**1**). During



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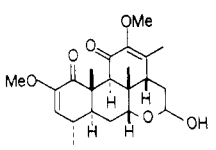

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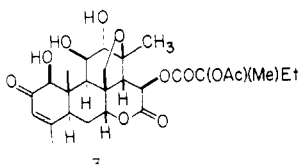
the early 1950s, Robertson and co-workers succeeded in characterizing the two major constituents of quassia wood, quassin (**1**) and neoquassin (**2**).[4] A decade later, after extensive studies, Valenta and co-workers[5] elucidated by classical methods the structures of quassin and neoquassin, as major constituents of *Simaroubaceae*. Since the structure of quassin was put forth over 20 years ago, numerous highly oxygenated quassinoids[6,7] have been isolated from *Simaroubaceae* [cf. quassimarin (**3**)[8] and glaucarubolone (**4**)[9]]. Extensive studies have been carried out on



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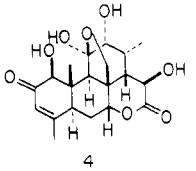

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quassinoid bitter principles, since these naturally occurring substances possess potent cytotoxic properties.[10]

The highly oxygenated tetracyclic carbon skeleton of quassin coupled with its complex stereochemical arrangement of carbon atoms has stimulated a great deal of synthetic activity.[11] Early

(1) On leave from the University of Pavia, 1979–1980. Recipient of a fellowship from the Consiglio Nazionale delle Ricerche d'Italia.

(2) Winckler, F. L. *Rep. Pharm.* **1835**, *4*, 85.

(3) Clark, E. P. *J. Am. Chem. Soc.* **1937**, *59*, 927, 2511.

(4) (a) London, E.; Robertson, A.; Worthinghton, H. *J. Chem. Soc.* **1950**, 3431. (b) Beer, R. J. S.; Jaquiss, D. B. G.; Robertson, A.; Savige, W. E. *Ibid.* **1954**, 3672. (c) Hanson, K. R.; Jaquiss, D. B.; Lamberton, J. A.; Robertson, A.; Savige, W. E. *Ibid.* **1954**, 4238. (d) Beer, R. J. S.; Hanson, K. R.; Robertson, A. *Ibid.* **1956**, 3280. (e) Beer, R. J. S.; Dutton, B. J.; Jaquiss, D. B.; Robertson, A.; Savige, W. E. *Ibid.* **1956**, 4850.

(5) (a) Valenta, Z.; Papadopoulos, S.; Podesva, C. *Tetrahedron* **1961**, *15*, 100. (b) Valenta, Z.; Gray, A. H.; Orr, D. E.; Papadopoulos, S.; Podesva, C. *Ibid.* **1962**, *18*, 1433. (c) Carman, R. M.; Ward, A. D. *Tetrahedron Lett.* **1961**, 317; (d) *Aust. J. Chem.* **1962**, *15*, 805.

(6) The term quassinoid refers to chemically related Simaroubaceae constituents, which form the bitter principles of the quassin group.

(7) For an excellent review on quassinoids, see: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

(8) Kupchan, S. M.; Streelman, D. R. *J. Org. Chem.* **1976**, *41*, 3481.

(9) Gaudemer, A.; Polonsky, J. *Phytochemistry* **1965**, *4*, 149.

(10) Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; Ziegler, M. F.; Sigel, C. W. *J. Org. Chem.* **1975**, *40*, 648. Kupchan, S. M.; Lacadie, J. A. *Ibid.* **1975**, *40*, 654. Kupchan, S. M.; Lacadie, J. A.; Howie, G. A.; Sickles, B. R. *J. Med. Chem.* **1976**, *19*, 1130. Wall, M. E.; Wani, M. C. *Annu. Rev. Pharmacol. Toxicol.* **1977**, *17*, 117; *J. Med. Chem.* **1978**, *21*, 1186. Wani, M. C.; Taylor, H. L.; Thompson, J. B.; Wall, M. E.; McPhail, A. T.; Onan, K. D. *Tetrahedron* **1979**, *35*, 17.

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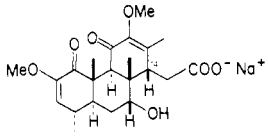
degradative studies established that of the seven chiral centers present in quassin, only four [C(5), C(7), C(8), and C(10)] need be addressed during the preliminary synthetic planning. It has been shown by Robertson[4c-e] that treatment of quassin with aqueous base under mild conditions gives rise to **5**, which, upon



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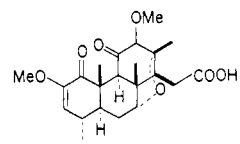

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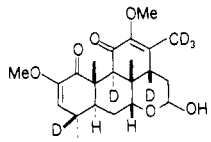
exposure to carbon dioxide, regenerates quassin. However, treatment of quassin with aqueous base at elevated temperatures induces epimerization at C(14) which gives way to pseudoquassinolic acid **6**[5b] via Michael addition of the C(7) α-oriented hydroxyl to the ring C diosphenol. It was also established during the early structure elucidation studies that treatment of naturally occurring neoquassin with sodium methoxide in deuterated methanol gives rise to the hexadeuterated neoquassin **7**.[5a] In



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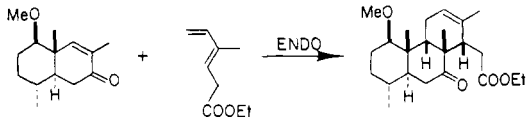
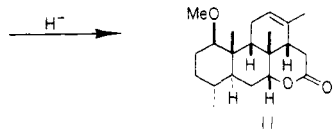
addition, it was shown that treatment of neoquassin with silver oxide gives rise to quassin.[4]

Two significant pieces of information can be derived from the early structure elucidation studies conducted independently by Robertson and Valenta. First of all, neoquassin emerges as the logical precursor to quassin. Second, and more importantly, the stereochemistry at C(4), C(9), and C(14) can, if necessary, be established during the final stages of the synthesis since these centers are in their most stable conformation. Note that the configuration at C(14) is only in its most stable arrangement when the ring D δ-lactone or its equivalent is in place.

Our initial plan called for application of an intermolecular Diels–Alder strategy to construct the ABC ring system of quassin. Cycloaddition of dienophile **8** with ethyl (*E*)-4-methyl-3,5-hexadienoate (**9**) was expected to give rise to Diels–Alder adduct **10**.



8 9 10



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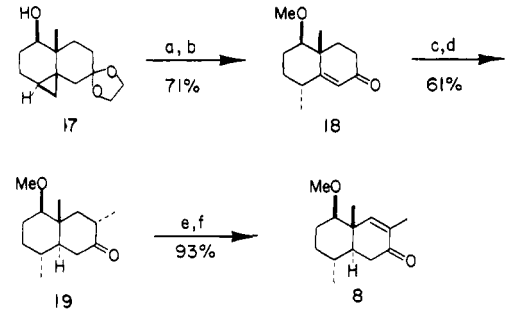
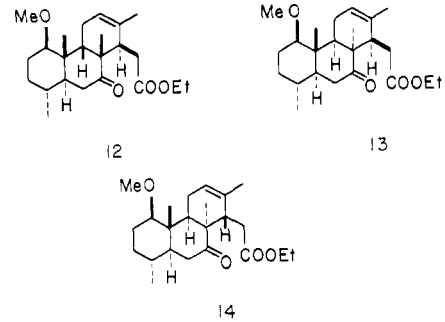
Hydride reduction and subsequent lactonization would provide the intact carbon framework of quassin. With the exception of the configuration at C(9), the Diels–Alder strategy would establish six of the seven stereocenters found in quassin.

Careful scrutiny of the Diels–Alder strategy reveals that there are, in principle, four possible adducts that can be derived from the cycloaddition of octalone **8** with ethyl (*E*)-4-methyl-3,5-hexadienoate (**9**). Approach of the diene from the α-face of **8** can generate the desired endo adduct **10** and/or the exo adduct **12**. On the other hand, attack from the β-face of **8** leads to adducts **13** (endo) and **14** (exo).

Scheme I. Preparation of Dienophile 8[a]



[a] (a) NaH, THF, MeI; (b) 70% $HClO_4$, CH_2Cl_2, 0 (1 h) → 25 °C (3 h); (c) LDA, THF, MeI, −78 → 0 °C; (d) Li, NH_3, *t*-BuOH, THF; (e) $C_6H_5N(Me)_3Br_3$, THF, 0 °C; (f) Li_2CO_3, LiBr, DMF, 140 °C.

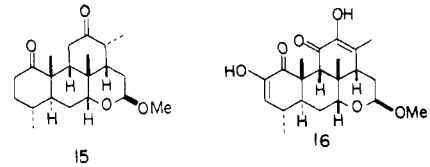


12 13 14

It was our contention that the presence of the methyl group at C(10) in dienophile **8** would seriously interfere with approach of the diene from the β-face, hence eliminating formation of adducts **13** and **14**. There were, however, serious reservations about whether the endo adduct **10** or exo adduct **12** would predominate as a consequence of diene **9** interacting with the α-face of **8**. Note that formation of endo adduct **10** sets up a serious interaction between the diene system and the C(5) proton.

With regards to the reduction of the C(7) keto function in adduct **10**, there are two factors that we felt would ensure that hydride reduction would give rise to tetracyclic lactone **11** with the proper configuration at C(7). The cis-fused nature of the BC ring system coupled with the presence of an axial substituent at C(14) should induce hydride attack on the C(7) carbonyl from the convex (β) face of the molecule, thereby guarantying formation of tetracyclic lactone **11**.

Our proposal to transform tetracyclic lactone **11** into quassin was to proceed via diketone **15**. Oxidation of **15** to bis(diosphenol)



15 16

16 followed by equilibration at C(9), methylation, and transformation of the protected lactol into a δ-lactone would provide access to quassin.

Results

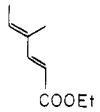
Preparation of Dienophile 8 and Ethyl (*E*)-4-Methyl-3,5-hexadienoate (9). The key intermediate dienophile **8**, mp 37–38 °C,

(11) (a) Stojanac, N.; Sood, A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 619. (b) Koch, H. J.; Pfenninger, H.; Graf, W. *Helv. Chim. Acta* **1975**, *58*, 1727. (c) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685; *J. Org. Chem.* **1977**, *42*, 1613; (e) *Synth. Commun.* **1977**, *7*, 293; (f) *J. Org. Chem.* **1977**, *42*, 3584. (g) Snitman, D. L.; Tsai, M. Y.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 195. (h) Stojanac, N.; Stojanac, Z.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3346. (i) Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (j) Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. (k) Grieco, P. A.; Vidari, G.; Ferrino, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, 1619. (l) Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (m) Okano, M.; Lee, K.-H. *J. Org. Chem.* **1981**, *46*, 1138. (n) Kametani, T.; Chihiro, M.; Honda, T.; Fukumoto, K. *Chem. Pharm. Bull.* **1980**, *28*, 2468. (o) Mandell, L.; Lee, D. E.; Courtney, L. F. *J. Org. Chem.* **1982**, *47*, 610. (p) Fukumoto, K.; Chihiro, M.; Shiratori, Y.; Ihara, M.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1982**, 2973. (q) Kraus, G. A.; Taschner, M.; Shimagaki, M. *Ibid.* **1982**, *47*, 4271. (r) Voyle, M.; Kyler, K. S.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 470. (s) Voyle, M.; Dunlap, N. K.; Watt, D. S.; Anderson, O. P. *Ibid.* **1983**, *48*, 3242. (t) Pariza, R. J.; Fuchs, P. L. *Ibid.* **1983**, *48*, 2306.

was prepared via a six-step sequence (Scheme I) from decalol **17**, which we had synthesized previously in connection with the total synthesis of eriolanin and eriolangin.[12] Despite the problems often associated with cleaving methyl ethers, we proceeded to prepare the methyl ether of **17**, which upon treatment with 70% perchloric acid results in simultaneous cleavage of the ketal and the cyclopropane ring and subsequent equilibration at C(4) [quassin numbering] with formation of octalone **18**. Use of 10% hydrochloric acid in tetrahydrofuran at reflux resulted in only loss of the ketal. That equilibration at C(4) had occurred was made obvious by examination of the ^{1}H NMR spectra of **18**, which revealed the olefinic proton as a doublet centered at δ 5.78 with J = 1.8 Hz.[13] Had equilibration not taken place, the olefinic proton should have appeared as a singlet with a width at half height equal to 1.5–1.8 Hz.

Generation of the kinetic enolate of **18** and methylation with methyl iodide gave the corresponding C(8) methylated octalone, which was subjected directly to treatment with lithium in liquid ammonia. Decalone **19**, mp 51–52 °C, was realized in 77% overall yield from **18**. Regioselective bromination of octalone **19** and subsequent dehydrobromination provided crystalline dienophile **8** in 93% yield.

Ethyl (*E*)-4-methyl-3,5-hexadienoate (**9**) was prepared in a straightforward manner in 61% overall yield by condensation of commercially available tiglic aldehyde with the sodium salt of triethylphosphonoacetate in benzene followed by deconjugation of the resultant $\alpha,\beta,\gamma,\delta$-unsaturated ester **20**. Analysis of the



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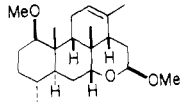

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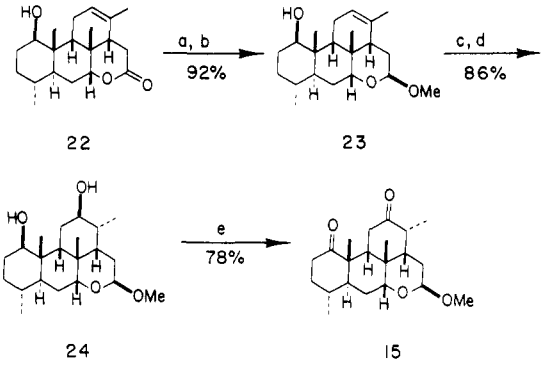
^{1}H NMR of **9** clearly established that we were dealing with a homogeneous substance possessing the desired trans olefinic geometry.

Preparation of Tetracyclic Diketone 15 via an Intermolecular Diels–Alder Reaction. Initial attempts to carry out the cycloaddition of dienophile **8** with diene **9** under standard thermal conditions in hydrocarbon solvents (benzene, toluene, xylene) proved fruitless. At room temperature or slightly above no reaction occurred. However, at elevated temperatures, in refluxing benzene or toluene, the starting materials were completely consumed with no trace of any Diels–Alder adducts being present. In an effort to promote the Diels–Alder reaction between **8** and **9**, we resorted to Lewis acid catalysis. Initial use of boron trifluoride etherate in benzene at ambient temperature gave rise to a complex mixture of products. We next turned our attention to aluminum chloride. Use of 1.0 equiv of aluminum chloride in benzene resulted in rapid and extensive polymerization of the diene. On the other hand, when only 0.25 equiv of aluminum chloride was employed in benzene containing 3-*tert*-butyl-4-hydroxy-5-methylphenyl hydrosulfide, the reaction of **8** with excess diene **9** gave rise after 66 h to a 62% yield of Diels–Alder adduct **10**, mp 87–88 °C, with no trace of any other Diels–Alder adducts being present.

Similar results were obtained when ethyl aluminum dichloride was substituted for aluminum chloride. Yields were generally 60–70% of isolated chromatographically pure crystalline **10**. The stereochemistry of adduct **10** was originally surmised from the method of preparation, with additional support from the NMR spectrum (see Experimental Section). Unequivocal support was obtained by single-crystal X-ray analysis of tetracyclic lactone **11**,[14] mp 160–161 °C, derived from **10** by reduction with sodium borohydride in methanol and subsequent lactonization. The formation of **11** proceeded as anticipated in 89% yield. Approximately 5–7% of methyl acetal **21** was isolated. Use of absolute ethanol in place of methanol gave rise to only a 44% yield of lactone **11**, along with 3% of the lactol derived from **11** and 14% of the corresponding *O*-ethyl-protected lactol.

Scheme II. Preparation of Tetracyclic Diketone **15**[a]



[a] (a) *i*-Bu$_2$AlH, PhCH$_3$, −78 °C; (b) MeOH, HCl; (c) B_2H_6, THF; (d) OH^-, H_2O_2; (e) CrO_3 2py.

With six of the seven chiral centers of quassin embodied in tetracyclic lactone **11**, we set out to transform **11** into diketone **15** (Scheme II), which would set the stage for completion of the total synthesis of quassin. The early observations by Valenta regarding the base-promoted conversion of quassin into pseudoquassinolic acid (cf. **1** → **6**)[5b] suggested that the ring D δ-lactone unit would have to be masked in order to permit the necessary inversion of configuration at C(9). Toward this end, methyl ether **11** was demethylated using a modification of the procedure developed by Fujita.[16] Use of ethanedithiol in the presence of boron trifluoride etherate and hydrochloric acid provided in 82% yield the crystalline tetracyclic hydroxy lactone **22**, mp 213–214 °C, which represents a versatile intermediate for elaboration into quassinoids. In this regard, tetracyclic lactone **22** has been transformed into *dl*-quassin[17] (vide infra) and *dl*-castelanolide.[18]

Prior to hydroboration of the C(12)–C(13) olefinic bond, the lactone carbonyl was reduced and the resultant lactol was subjected to treatment with a catalytic amount of concentrated hydrochloric acid in methanol, giving rise to protected lactol **23**, mp 161–163 °C. Hydroboration of **23** and subsequent workup with alkaline hydrogen peroxide afforded (86%) crystalline diol **24**, which upon Collins oxidation provided access to tetracyclic diketone **15**, mp 167–168 °C.

Initial Attempts To Transform Tetracyclic Diketone 15 into *dl*-Quassin. At this stage in our quest for *dl*-quassin, the conversion of diketone **15** into quassin appeared to hinge on three critical operations: (1) elaboration of the fully methylated diosphenol functionality in rings A and C via oxidation adjacent to the C(1) and C(12) carbonyl groups, (2) inversion of configuration about C(9), and (3) unmasking of the ring D δ-lactone functionality. Prior to examining the reaction of diketone **15** with Bredereck's reagent [tris(dimethylamino)methane][19] we examined in a preliminary study model system **25**. Treatment of **25** with excess Bredereck's reagent generated the enamino ketone **26**, which, when subjected to photooxidation,[20] gave diosphenol **27** in 77% overall yield. Encouraged by the above experiment, we immediately

(12) Grieco, P. A.; Oguri, T.; Gilman, S. *J. Am. Chem. Soc.* **1980**, *102*, 5886.

(13) Collins, D. J.; Hobbs, J. J.; Sternhell, S. *Aust. J. Chem.* **1963**, *16*, 1030.

(14) Crystals of racemic compound **11** are monoclinc, space group $P2_1/n$, a = 8.522 (2) Å, b = 22.773 (4) Å, c = 10.190 (2) Å; β = 111.32 (1)°; V = 1842.4 (6) Å^3; ρ_c = 1.20 g cm^{-3} (for Z = 4). A total of 3240 reflections were measured, of which 1713 were determined to be observable, $F_o^2 > 3\sigma(F_o^2)$. The structure was determined by routine multisolution direct methods[15] and refined to a current residual of R = 0.066.

(15) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

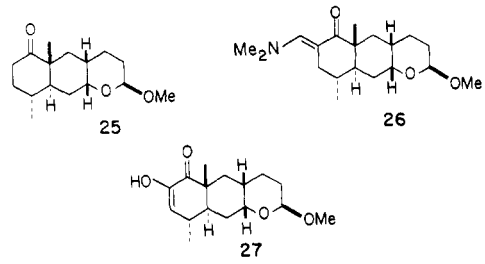
(16) Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2237.

(17) For a preliminary account of this work, see: Grieco, P. A.; Ferriño, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586.

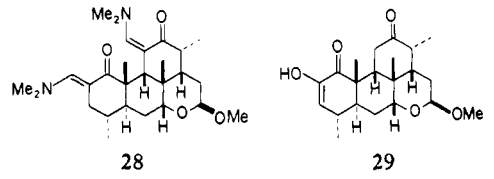
(18) Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J. Y. *J. Org. Chem.* **1981**, *47*, 601.

(19) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.

(20) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1978**, *43*, 3238; *J. Am. Chem. Soc.* **1976**, *98*, 7868.

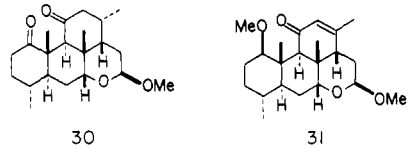


proceeded to examine the reaction of **15** with excess tris(dimethylamino)methane. Without purification the alledged bis(enamino ketone) **28** was subjected to photooxidation. Workup

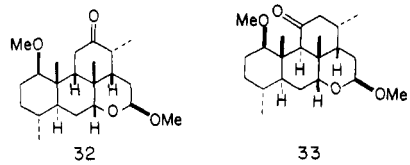


provided none of the desired bis(diosphenol) **16**, as was clearly evidenced by examination of the ^1H NMR and IR spectra of the crude reaction product. The spectra of the purified product, which was obtained in 25% isolated yield, were consistent with structure **29**. In retrospect the formation of **29** is not surprising in view of the severe steric crowding about the C(11) carbon in diketone **15**.

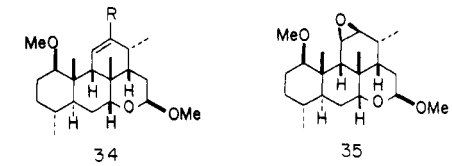
Development of a Mild Method for Elaborating the Diosphenol Structural Unit. Frustrated by our initial lack of success in transforming tetracyclic diketone **15** into *dl*-quassin, we set out to explore the feasibility of employing tetracyclic diketone **30**, with



the proper configuration at C(9), as a precursor to *dl*-quassin. The fact that C(2) and C(12) in **30** are both readily accessible was encouraging and appeared to offer a solution to our dilemma. Efforts to prepare **30** initially focused on trying to transform **11** into **31** via allylic oxidation and subsequent manipulation of the lactone moiety. All attempts to introduce oxygen at C(11) met with no success. Similarly unsuccessful were attempts to transform olefin **21**, prepared in 96% yield from **11** by reduction (i-Bu_2AlH, $PhCH_3$, −78 °C) and exposure to methanol containing hydrochloric acid, into **31**. In an effort to overcome the above difficulties, we transformed [(1) B_2H_6, THF; (2) OH^-, H_2O_2; (3) CrO_3·2Py] in straightforward fashion olefin **21** into ketone **32** with

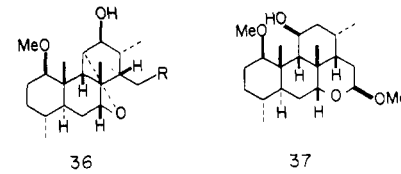


the expectation of being able to carry out a 1,2-carbonyl transposition on **32** so as to give rise to tetracyclic ketone **33** after inversion of configuration at C(9). Once again, all our efforts to transform **32** into **33** were unsuccessful. Treatment of **32** with lithium diisopropylamide in tetrahydrofuran followed by addition of either diphenyl disulfide or dimethyl disulfide gave upon workup only recovered **32**. Efforts to hydroxylate the enolate with the molybdenum peroxide reagent MoO_5·py·HMPA[21] (py = pyridine) gave no reaction. Attempts to formylate **32** were also unsuccessful. Exposure of **32** to either tris(dimethylamino)methane or bis(dimethylamino)-*tert*-butoxymethane gave only recovered starting material. Trapping of the kinetic enolate derived from **32** with bis(dimethylamino) phosphorochloridate in tetrahydrofuran gave in 50% yield enol phosphoramide **34** (R = $OP(O)NMe_2$), which



upon treatment with lithium in liquid ammonia provided olefin **34** (R = H).[22] The method of choice for preparing **34** involved treatment of the tosylhydrazone derived from **32** with excess butyllithium. This two-step sequence provided **34** (R = H) as a crystalline material, mp 79–80 °C, in 90–95% overall yield.

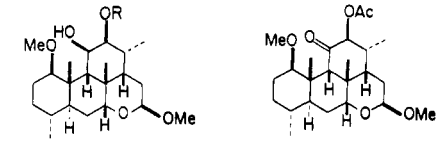
With the availability of olefin **34** in excellent overall yield from ketone **32**, we examined its epoxidation with a variety of peracids only to find that very little of the desired β-epoxide **35** could be isolated due to extensive decomposition of **35** under the reactions conditions. Fortunately use of Payne's procedure (50% H_2O_2, PhCN, MeOH, $KHCO_3$)[23] provided in 83% yield epoxide **35**, mp 129–130 °C. Epoxide **35** proved to be exceedingly sensitive to acid. For example, brief exposure of **35** to hydrochloric acid in aqueous acetone gives rise to a 92% yield of the novel aldehyde **36** (R = CHO). The formation of **36** is not surprising in view



of the fact that Dreiding models reveal the close proximity of the C(7) oxygen atom to the C(11) carbon atom.[24]

The availability of epoxide **35** prompted us to examine the possibility of delivering hydride attack at C(12) so as to give rise to alcohol **37**. Treatment of **35** with lithium aluminum hydride in refluxing tetrahydrofuran gave none of the desired alcohol **37**. Instead, a 60% yield of the crystalline, rearranged methyl ether **36** (R = CH_2OMe), mp 163–164 °C, was isolated. The structure of **36** (R = CH_2OMe) was unambiguously established by single-crystal X-ray analysis.[25] Alcohol **37** was finally realized in modest yield (51%) by treatment of epoxide **35** with lithium in ethylenediamine.

The unanticipated difficulties associated with epoxide **35** and the poor yield of **37** from **35**, led us to retreat to olefin **34**. Treatment of **34** with osmium tetroxide in pyridine provided in 88% yield the crystalline diol **38** (R = H), mp 122–124 °C. Based on our experiences above, there was little doubt in our minds that we could selectively acetylate the C(12) hydroxyl. Indeed exposure of **38** (R = H) to acetic anhydride in pyridine afforded in excellent yield (90%) crystalline monoacetate **38** (R = Ac), mp 164–165



°C, whose structure followed from the ^1H NMR spectrum. Collins

(21) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

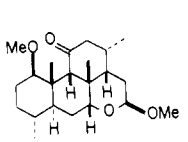
(22) Cf.: Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(23) Payne, G. B.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 651. Payne, G. B.; Deming, P. H.; Williams, P. H. *Ibid.* **1961**, *26*, 659.

(24) Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C.; Williams, E. *Tetrahedron Lett.* **1981**, *22*, 1071.

(25) Compound **36** (R = CH_2OMe) crystallizes in space group $P2_1/n$ with a = 11.997 (2) Å, b = 10.753 (2) Å, c = 16.056 (3) Å, and β = 109.86 (2)° at −182 °C; C_{calc} = 1.243 gm/cm^3 for Z = 4. A continuous θ–2θ scan at a rate of 3°/min over a range of 2° + dispersion and 5-sec background counts was used to collect the 2534 unique amplitudes on a Picker goniostat. The structure was solved by direct methods and refined by full-matrix least squares to yield final residuals of R_F = 0.067 and R_{wF} = 0.059.

oxidation of **38** (R = Ac) furnished (83%) keto acetate **39**, mp 213–215 °C, which once again offered the opportunity to make progress toward quassin. Cleavage of the acetoxy ketone with calcium in liquid ammonia provided access to ketone **40** in 71%



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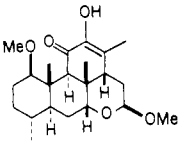
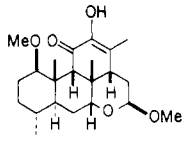


41

yield. Treatment of **40** with sodium methoxide in dimethyl sulfoxide (50–55 °C) gave rise to the equilibrated ketone **33** in 68% yield.

It was during an attempt to equilibrate acetoxy ketone **39** with base in dimethyl sulfoxide that a remarkable reaction was discovered.[26] Treatment of ketone **39** with sodium methoxide in dimethyl sulfoxide at 55 °C for 30 min gave rise upon TLC analysis to a minor UV active spot, which appeared to increase with time and temperature. When the temperature was raised to 95 °C and held at that temperature for 1 h, TLC analysis indicated the clear transformation of keto acetate **39** into this UV-active product. ^{1}H NMR analysis (220 MHz in $CDCl_3$) of the isolated material, mp 161–163 °C, revealed a new one-proton singlet centered at δ 6.10, which interchanged with deuterium oxide, the presence of the olefinic methyl group at δ 1.77, and a new one-proton singlet at δ 2.76. The infrared data coupled with the ^{1}H NMR data clearly suggested the presence of a diosphenol unit in ring C. Two plausible structures, **41** and **42**,



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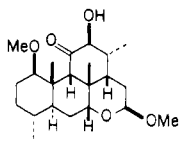
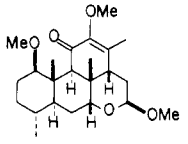


43

emerge from the spectral data. Unfortunately, ^{1}H NMR did not allow us to distinguish between these structures. The *structure of the unknown product was unambiguously established as* **41** by single-crystal X-ray analysis.[26] With this welcome stroke of good luck, we turned our attention to defining the scope of the diosphenol forming reaction. We very quickly established that the 12-hydroxy-11-keto tetracyclic compound **43**, readily available in 58% yield by treatment of the kinetic enolate (LDA, THF) derived from **40** with MoO_5·py·HMPA[21] (−78 → 0 °C), upon exposure to sodium methoxide in methanol and dimethyl sulfoxide for 30 min at 55 °C and for 1 h at 95 °C followed by cooling to 10 °C and addition of methyl iodide provided in 82% isolated yield the diosphenol *O*-methyl ether **44**, mp 150–151 °C. This re-



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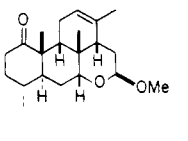
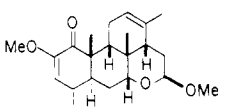


45

markable reaction is dependent upon having oxygen present. However, attempts to carry out the transformation of **43** to **44** in an atmosphere of oxygen lead to decomposition of the intermediate diosphenol. Prior to describing the transformation by which tetracyclic diketone **15** was converted into *dl*-quassin, we relate the results of one additional experiment. It was our contention that if ketone **45**, readily available from alcohol **23**, could be transformed smoothly into diosphenol *O*-methyl ether **46**, then the stage would be set for the critical series of reactions leading from **15** to *dl*-quassin. Oxygenation of the enolate derived from ketone **45** (LDA, THF, −78 °C) with MoO_5·py·HMPA at 0 °C



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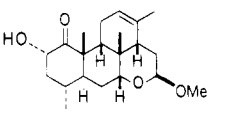
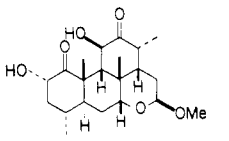


47

proceeded smoothly giving rise to α-hydroxy ketone **47** in 57% yield.

Treatment of **47** with sodium methoxide in methanol and dimethyl sulfoxide as described above followed by methylation gave in 93% yield tetracyclic diosphenol *O*-methyl ether **46**, mp 151–152 °C.

Synthesis of *dl*-Quassin. Based on the availability of tetracyclic diketone **15** and the methodology described above, we were obliged to proceed with completing the synthesis of *dl*-quassin. Oxygenation of the dianion derived from diketone **15** with MoO_5·py·HMPA (10.0 equiv, 0 °C, 15 min) afforded as the major product in 35% isolated yield the crystalline bis(α-hydroxy ketone) **48**, mp 215–218 °C.[27] Initially tetracyclic compound **48** was



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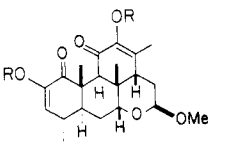

49

smoothly transformed (50% yield) upon treatment with sodium methoxide in dimethyl sulfoxide [55 °C (30 min), 95 °C (1 h)] into bis(diosphenol) **49** (R = H), mp 207–209 °C, which was, in a subsequent step, methylated (NaOMe, Me_2SO, MeI) giving rise in 65% yield to neoquassin β-*O*-methyl ether **49** (R = Me). The conversion of **48** into **49** (R = Me) could be accomplished in a single operation in 57% overall yield (see Experimental Section).

Selective hydrolysis [HOAc–HOH (3:2), reflux 25 min] of the protected lactol in **49** (R = Me) afforded crystalline racemic neoquassin (**2**) identical with a sample of natural neoquassin by comparison of spectral properties [^{1}H NMR (220 MHz), IR] and thin-layer mobility in several solvent systems. Oxidation (Fetizon's reagent,[28] benzene, 2-h reflux) of synthetic neoquassin provided in 77% yield from **49** (R = Me) racemic quassin, mp 189–190 °C. Synthetic quassin (**1**) was identical with an authentic sample by TLC, IR, and ^{1}H NMR (220 MHz).

Experimental Section

[4a*R*-(4aβ,5β,5β,8α)]-4,4a,5,6,7,8-Hexahydro-4a,8-dimethyl-5-methoxy-2(3*H*)-naphthalenone (18). A solution of 10.3 g (43.3 mmol) of the known alcohol **17**[12] in 30 mL of tetrahydrofuran was added to a suspension of 12.4 g (258 mmol) of sodium hydride (50% oil dispersion) in tetrahydrofuran at room temperature under argon. After the suspension was refluxed for 30 min, 14.4 mL (231 mmol) of methyl iodide and 3 g (8 mmol) of tetra-*n*-butylammonium iodide were added at room temperature. The reaction mixture was allowed to reflux for 1 h. The suspension was cooled to room temperature, and the inorganic salts were filtered. The solvent was evaporated, and the residue was diluted with ether and was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate in vacuo provided a crude residue, which was dissolved in 500 mL of methylene chloride and cooled to 0 °C prior to the dropwise addition of 30 mL of 70% perchloric acid. The reaction mixture was stirred for 1 h at 0 °C and 3 h at room temperature. The excess acid was neutralized by the careful addition of solid sodium bicarbonate. The inorganic salts were filtered and the organic layer was washed with a saturated sodium bicarbonate solution. The aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried over anhydrous magnesium sulfate. After filtration and concentration in vacuo, the crude product was chromatographed on 500 g of silica gel. Elution with hexane–ether, 4:1, gave 6.42 g (71%) of octalone **18** as a pale yellow oil: R_f 0.34, hexane–ether, 2:1; IR (CCl_4) 2967, 2933, 2850,

(26) Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 1022.

(27) In addition, ca. 10% of an isomeric mixture of bis(α-hydroxy ketones) was isolated, which were subsequently transformed into *dl*-quassin using the methodology described in the text.

(28) Fetizon, M.; Golfier, M. *C. R. Acad. Sci., Ser. C* **1968**, *267*, 900.

2808, 1671, 1610, 1458, 1417, 1372, 1360, 1325, 1292, 1267, 1233, 1200, 1183, 1167, 1140, 1100, 1008, 983, 950, 879, 850 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 5.78 (d, 1 H, J = 1.8 Hz), 3.37 (s, 3 H), 2.88 (dd, 1 H, J = 11, 5 Hz), 1.2–2.5 (m, 9 H), 1.17 (s, 3 H), 1.05 (d, 3 H, J = 6.5 Hz); high-resolution MS, calcd for $C_{13}H_{20}O_2$ 208.1460, found 208.1456.

[3*S*-(3α,4aβ,5β,8α,8aα)]-3,4,4a,5,6,7,8,8a-Octahydro-3,4a,8-trimethyl-5-methoxy-2(1*H*)-naphthalenone (19). To a solution of 8.06 mL (57.5 mmol) of diisopropylamine in 300 mL of tetrahydrofuran at 0 °C was added 35.95 mL (57.5 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. The solution was cooled to −78 °C and 10.88 g (52.3 mmol) of octalone **18** in 15 mL of tetrahydrofuran was added. After stirring for 1 h at −78 °C and 1.5 h at 0 °C, 10 mL (161 mmol) of methyl iodide was added dropwise. Stirring was continued at room temperature for 30 min. The reaction was quenched with water, diluted with ether, and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded an oily residue, which was directly chromatographed on 900 g of silica gel. Elution with hexane–ether (10:1) gave 9.2 g (79%) of [3*S*-(3α,4aβ,5β,8α)]-4,4a,5,6,7,8-hexahydro-3,4a,8-trimethyl-5-methoxy-2(3*H*)-naphthalenone [R_f 0.57, hexane–ether, 1:1; IR (film) 2967, 2942, 2917, 2875, 2858, 2817, 1679, 1620, 1471, 1458, 1379, 1362, 1354, 1333, 1300, 1242, 1221, 1204, 1196, 1179, 1142, 1100, 1067, 983, 962, 892, 879, 863, 850 cm^{-1}; high-resolution MS, calcd for $C_{14}H_{22}O_2$ 222.1619, found 222.1618], which was used directly in the next reaction.

A solution of 6.3 g (28.37 mmol) of the above octalone in 80 mL of anhydrous tetrahydrofuran was added to a solution of 1.18 g of lithium (169.7 mmol) in 1.2 L of liquid ammonia containing 4.0 mL of *tert*-butyl alcohol. After 2 h the reaction was quenched by the addition of butadiene. After addition of 1 g of solid ammonium chloride, the ammonia was evaporated leaving a residue, which was taken up in 500 mL of ether and 25 mL of brine. The aqueous phase was extracted with ether, and the combined ether extracts were dried over anhyhdrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo provided an oily residue, which was directly chromatographed on 600 g of silica gel. Elution with hexanes–ether (7:1) afforded 4.85 g (77%) of decalone **19** as a white crystalline solid: mp 51–52 °C; R_f 0.57, hexane–ether, 1:1; IR (film) 2968, 2925, 2900, 2867, 2842, 2808, 1708, 1467, 1387, 1362, 1342, 1300, 1283, 1242, 1225, 1200, 1140, 1100, 1067, 1035, 1021, 1000, 983, 958 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 3.32 (s, 3 H), 2.70 (dd, 1 H, J = 12, 5 Hz), 1.07 (s, 3 H), 1.0 (d, 3 H, J = 6 Hz), 0.77 (d, 3 H, J = 6 Hz); high-resolution MS, calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1775.

[4a*R*-(4aβ,5β,8α,8aα)]-4a,5,6,7,8,8a-Hexahydro-3,4a,8-trimethyl-5-methoxy-2(1*H*)-naphthalenone (8). A solution of 57.64 g (153.3 mmol) of phenyltrimethylammonium tribromide in 760 mL of anhydrous tetrahydrofuran was added dropwise to a cooled (0 °C) solution of 31.8 g (142.0 mmol) of ketone **19** in 300 mL of anhydrous tetrahydrofuran under nitrogen. The reaction mixture was stirred 10 min at room temperature, and the solvent was evaporated under reduced pressure leaving a residue, which was diluted with 500 mL of ether and 100 mL of brine. The aqueous phase was extracted with ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo provided a residue, which was dissolved in 200 mL of *N*,*N*-dimethylformamide, which was added dropwise to a suspension of 26.1 g (300 mmol) of lithium bromide and 33.34 g (451 mmol) of lithium carbonate in 210 mL of anhydrous *N*,*N*-dimethylformamide under nitrogen. The reaction mixture was stirred for 20 min at 140 °C. After the reaction mixture was allowed to cool to room temperature, the inorganic solids were filtered and the filtrate was dissolved in 500 mL of hexane and 250 mL of water. The aqueous phase was extracted with hexane and the combined hexane extracts were dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo afforded an oily residue, which was chromatographed on 600 g of silica gel. Elution with hexane–ether (10:1) afforded 29.3 g (93%) of octalone **8** as a white crystalline solid: mp 37–38 °C; R_f 0.67, hexane–ether, 1:1; IR (CCl_4) 3018, 2975, 2945, 2925, 2892, 2875, 2842, 2818, 1671, 1462, 1458, 1446, 1417, 1379, 1358, 1335, 1275, 1258, 1196, 1171, 1137, 1100, 1067, 1008, 992, 983, 962, 942, 921, 879, 850 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 7.03 (q, 1 H, J = 1.5 Hz), 3.38 (s, 3 H), 2.90 (dd, 1 H, J = 11, 5 Hz), 1.75 (d, 3 H, J = 1.5 Hz), 1.0 (s, 3 H), 0.82 (d, 3 H, J = 6 Hz); high-resolution MS, calcd for $C_{14}H_{22}O_4$ 222.1619, found 227.1620. An analytical sample was prepared by recrystallization from pentane. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.52; H, 9.92.

Ethyl (*E*)-4-Methyl-3,5-hexadienoate (9). To a suspension of 31.4 g (1.31 mol) of sodium hydride (50% oil dispersion) in 150 mL of dry benzene under nitrogen at room temperature was added dropwise 147 g (0.655 mol) of triethylphosphonoacetate. After stirring at room temperature for 1 h, 50 g (0.50 mol) of tiglic aldehyde was added dropwise. Stirring was continued at 65 °C for 15 min. The reaction was quenched at 15 °C by the addition of water. The intermediate α,β,γ,δ-unsaturated ester **20** was isolated by extraction with hexane. Distillation of the crude product gave 81.9 g (90%) of **20** as a colorless oil, bp 95 °C (1.1 mmHg), a portion of which was used directly in the next reaction.

To a solution of 15.9 mL (114.0 mmol) of diisopropylamine in 125 mL of tetrahydrofuran and 20.5 mL of hexamethylphosphoramide at −78 °C under nitrogen was added 71 mL (114.0 mmol) of a 1.6 M solution of *n*-butyllithium in hexane followed by the dropwise addition of 14 g (90.9 mmol) of unsaturated ester **20**. The reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched with a 50% aqueous acetic acid solution. The resulting mixture was diluted with 500 mL of ether and the aqueous phase was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate at atmospheric pressure provided an oily residue. Purification of the crude product by distillation gave 9.8 g (70%) of **9** as a colorless oil: bp 63 °C (6.5 mmHg); IR (film) 3091, 3033, 2983, 2925, 2900, 2875, 1729, 1641, 1608, 1442, 1387, 1369, 1317, 1250, 1220, 1160, 1092, 1058, 1025, 987, 942, 896, 842 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 6.35 (dd, 1 H, J = 18, 11 Hz), 5.68 (br, t, 1 H, J = 7.5 Hz), 5.15 (d, 1 H, J = 18 Hz), 5.05 (d, 1 H, J = 11 Hz), 4.15 (q, 2 H, J = 7 Hz), 3.20 (d, 2 H, J = 7.5 Hz), 1.78 (s, 3 H), 1.27 (t, 3 H, J = 7 Hz); high-resolution MS, calcd for $C_9H_{14}O_2$ 154.0994, found 154.0994.

Ethyl [1*S*-(1α,4aβ,4bβ,5β,8α,8aα,10aβ)]-1,4,4a,4b,5,6,7,8,8a,9,10,10a-Dodecahydro-5-methoxy-2,4b,8,10a-tetramethyl-10-oxo-1-phenanthreneacetate (10). To a solution of 400 mg (1.8 mmol) of octalone **8** in 1.0 mL of dry benzene containing 13 mg (0.036 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide and 60 mg (0.45 mmol) of anhydrous aluminum chloride cooled to 0 °C under argon was added in one portion 0.76 g (4.93 mmol) of diene **9**. The reaction mixture was stirred at room temperature in the dark for 66 h. The reaction was quenced by pouring into an ice-cooled 5% aqueous sodium bicarbonate solution. The product was extracted with methylene chloride (3 × 20 mL), and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on 80 g of silica gel. Elution with hexane–ether (9:1) provided 423 mg (62.4%) of tricyclic ketone **10** as a white crystalline solid: mp 87–88 °C; R_f 0.53, hexane–ether, 3:1; IR (CCl_4) 2965, 2925, 2865, 2810, 1733, 1690, 1455, 1440, 1403, 1368, 1340, 1320, 1300, 1280, 1245, 1228, 1190, 1170, 1150, 1085, 1030 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 5.74 (m, 1 H), 4.06 (q, 2 H, J = 7 Hz), 3.30 (s, 3 H), 3.08 (dd, 1 H, J = 11, 5 Hz), 1.74 (br s, 3 H), 1.24 (t, 3 H, J = 7 Hz), 1.24 (s, 3 H), 0.87 (s, 3 H), 0.84 (d, 3 H, J = 6.5 Hz); high-resolution MS, calcd for $C_{23}H_{36}O_4$ 376.2613, found 376.2607. An analytical sample was prepared by recrystallization from ethanol. Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.23; H, 9.61.

(1β,9β)-1-Methoxypicras-12-en-16-one (11). To a solution of 3.0 g (7.97 mmol) of Diels–Alder adduct **10** in 55 mL of absolute methanol cooled to 0 °C was added dropwise a solution of 3.1 g (82.0 mmol) of sodium borohydride in 110 mL of absolute methanol. The reaction mixture was stirred at room temperature for 3 h. Excess sodium borohydride was destroyed by the addition of 25 mL of acetone. The reaction mixture was acidified at 0 °C with concentrated hydrochloric acid. The reaction mixture was stirred at 0 °C for 1 h and was neutralized with solid sodium carbonate. The solvent was evaporated in vacuo, and the residue was diluted with 150 mL of methylene chloride and 50 mL of brine. The aqueous phase was extracted with methylene chloride, and the combined organic extracts were dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo afforded a residue, which crystallized from ether providing 2.16 g of tetracyclic lactone **11**: mp 159–160 °C; R_f 0.26, hexanes–ether, 1:1; IR ($CHCl_3$) 3000, 2950, 2925, 2880, 2850, 2817, 1738, 1467, 1450, 1392, 1379, 1346, 1333, 1316, 1287, 1267, 1242, 1192, 1146, 1133, 1117, 1083, 1046, 1025, 1000, 983, 960, 942, 860, 825 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.69 (m, 1 H), 4.16 (br s, 1 H), 3.25 (s, 3 H), 3.20 (dd, 1 H, J = 5, 11 Hz), 2.80 (dd, 1 H, J = 7.0, 15 Hz), 2.48 (dd, 1 H, J = 2, 15 Hz), 2.34 (d, 1 H, J = 7.0 Hz), 1.67 (br s, 3 H), 1.31 (s, 3 H), 1.06 (s, 3 H), 0.83 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ether, mp 160–161 °C. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.65; H, 9.63.

The mother liquors from above were concentrated under reduced pressure, and the residue was chromatographed on 20 g of silica gel. Elution with hexanes–ether, 3:1, provided in order of elution 195 mg of acetal **21** (R_f 0.81, hexanes–ether, 1:1), which was identical in all respects with an authentic sample (vide infra), and an additional 192 mg of tetracyclic lactone **11** (R_f 0.26). The yield for the formation of **11** was 89%.

(1β,9β)-1-Hydroxypicras-12-en-16-one (22). To a solution of 0.75 g (2.26 mmol) of (1β,9β)-1-methoxypicras-12-en-16-one (**11**) in 20 mL of ethanedithiol under argon was added 12 mL of boron trifluoride etherate

and 10 μL of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 15 h. The product was isolated by extraction with methylene chloride. The organic phase was washed with a 3 N sodium hydroxide solution. Excess ethanedithiol was codistilled with ethanol under reduced pressure. Chromatography of the residue on 100 g of silica gel (elution with hexanes–ether, 1:1) gave 0.59 g (82%) of tetracyclic alcohol **22** as a crystalline compound: mp 213–214 °C; R_f 0.42, hexanes–ether, 1:3; IR ($CHCl_3$) 3600, 3450, 3017, 2983, 2942, 2908, 2858, 1731, 1460, 1440, 1383, 1370, 1333, 1312, 1260, 1220, 1125, 1054, 1040, 1020, 982, 960, 900, 858, 820 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 5.71 (br d, 1 H, J = 6 Hz), 4.19 (br t, 1 H, J = 3 Hz), 3.73 (t, 1 H, J = 7.5 Hz), 1.70 (br s, 3 H), 1.37 (s, 3 H), 1.08 (s, 3 H), 0.83 (d, 3 H, J = 6 Hz); high-resolution MS, calcd for $C_{20}H_{30}O_3$ 319.2195, found 318.2181. An analytical sample was prepared by recrystallization from ether, mp 213–214 °C. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.22; H, 9.49.

(1β,9β,16β)-1-Hydroxy-16-methoxypicras-12-ene (23). To a solution of 3.4 g (10.7 mmol) of (1β,9β)-1-hydroxypicras-12-en-16-one (**22**) in 300 mL of anhydrous toluene at −78 °C under argon was added 24 mL of a 1 M solution of diisobutylaluminum hydride in hexane. The reaction was stirred at −78 °C for 30 min and was quenched by the slow addition of methanol followed by cold 10% aqueous hydrochloric acid. The aqueous phase was extracted with ether and the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo afforded crude lactol, which was used in the next reaction without further purification.

The above lactol was dissolved in 50 mL of methanol containing 0.1 mL of concentrated hydrochloric acid. The reaction mixture was stirred at 0 °C for 30 min, neutralized with solid sodium bicarbonate at room temperature, and filtered, and the solvent was evaporated under reduced pressure. The crude product was chromatographed on 200 g of silica gel. Elution with hexanes–ether (1:1) gave 3.28 g (92%) of acetal **23** as a white crystalline solid: mp 160–162 °C; R_f 0.81, hexane–ether, 1:2; IR ($CHCl_3$) 3600, 3455, 3000, 2950, 2930, 2920, 2880, 2835, 1463, 1441, 1390, 1375, 1365, 1220, 1177, 1164, 1105, 1060, 1045, 1035, 1030, 990, 960, 920, 908, 870, 865, 848 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.53 (br s, 1 H), 4.46 (dd, 1 H, J = 9, 5 Hz), 3.78 (t, 1 H, J = 6 Hz), 3.65 (br s, 1 H), 3.32 (s, 3 H), 1.65 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 0.83 (d, 3 H, J = 6 Hz). An analytical sample was prepared by recrystallization from ether, mp 161–163 °C. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.65; H, 10.59.

(1β,9β,12β,16β)-16-Methoxypicrasane-1,12-diol (24). To a solution of 3.2 g (9.57 mmol) of (1β,9β,16β)-1-hydroxy-16 methoxypicras-12-ene (**23**) in 150 mL of anhydrous tetrahydrofuran at 0 °C under argon was added 29 mL of a 1 M solution of diborane in tetrahydrofuran. The reaction was stirred at 0 °C for 30 min and at room temperature for 2 h. The reaction was cooled to 0 °C and was treated at 50 °C for 45 min with 29 mL of a 3 N sodium hydroxide solution and 29 mL of 30% hydrogen peroxide. After cooling to room temperature, the reaction mixture was diluted with 100 mL of water and was extracted with 3 × 150-mL portions of ether. The ether extracts were dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo provided crude product, which was chromatographed on 200 g of silica gel. Elution with hexanes–ether (1:2) gave 2.9 g (86%) of tetracyclic diol **24** as a white crystalline solid: R_f 0.38, hexanes–ether; IR ($CHCl_3$) 3595, 3360, 2992, 2950, 2925, 2900, 2870, 2830, 1478, 1460, 1444, 1394, 1375, 1365, 1343, 1325, 1285, 1235, 1210, 1183, 1135, 1090, 1055, 1020, 1007, 1000, 987, 980, 955, 930, 915, 885, 867, 832, 812 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 4.73 (d, 1 H, J = 5 Hz), 3.90 (br s, 1 H, OH), 3.59 (m, 4 H), 3.27 (s, 3 H), 1.14 (s, 3 H), 1.03 (d, 3 H, J = 6 Hz), 1.02 (s, 3 H), 0.84 (d, 3 H, J = 6 Hz). An analytical sample was prepared by recrystallization from ether, mp 172–173 °C. Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.40; H, 9.97.

(9β,16β)-16-Methoxypicrasane-1,12-dione (15). To a vigorously stirred solution of 23.9 mL of dry pyridine in 400 mL of dry methylene chloride cooled to 0 °C was added 14.75 g (147.5 mmol) of chromium trioxide. After 30 min at 0 °C, 49 g of celite was added. A solution of 2.6 g (7.37 mmol) of tetracyclic diol **24** in 40 mL of dry methylene chloride was added to the cooled flask containing the Collins reagent. After 30 min at 0 °C, 49 g of sodium hydrogen sulfate monohydrate was added. Stirring was continued for an additional 30 min followed by filtration of the reaction mixture through a pad of magnesium sulfate. The precipitate was thoroughly washed with ether. The combined organic washings were concentrated in vacuo on a rotary evaporator. The crude product was chromatographed on 100 g of silica gel. Elution with hexanes–ether (1:1) gave 2.01 g (78%) of dione **15** as a white crystalline solid: R_f 0.67, hexanes–ether, 1:3; IR ($CHCl_3$) 3000, 2967, 2945, 2930, 2900, 2830, 1705, 1442, 1375, 1210, 1132, 1080, 1045, 1025, 992, 950, 930, 900, 880 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 4.59 (t, 1 H, J = 5 Hz), 3.76 (br t, 1 H, J = 2.5 Hz), 3.30 (s, 3 H), 2.92 (m, 1 H), 1.27 (s, 3 H, 1.25 (s, 3 H), 1.02 (d, 3 H, J = 6.5 Hz), 0.99 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recyrstallization from ether–methanol (10:1), mp 167–168 °C. Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.38; H, 9.44.

(1β,9β,16β)-1,16-Dimethoxypicras-12-ene (21). To a rapidly stirred solution of 1.45 g (4.37 mmol) of lactone **11** in 200 mL of anhydrous toluene at −78 °C under argon was added dropwise 6.6 mL (6.6 mmol) of a 1.0 M solution of diisotbutylaluminum hydride in hexane. The reaction was stirred at −78 °C for 30 min and was quenched with methanol and cold 10% aqueous hydrochloric acid. The aqueous layer was extracted with ether. The combined ether extracts were washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo provided 1.46 g of crude lactol as a white foam, which was used in the next reaction without further purification.

A solution of 1.46 g of the above lactol in 150 mL of methanol and 50 μL of concentrated hydrochloric acid was stirred at 0 °C for 1.5 h. The reaction was quenched by the addition of solid sodium bicarbonate. Filtration followed by removal of the solvent under reduced pressure provided crude **21**, which was purified by column chromatography on 50 g of silica gel. Elution with hexanes–ether (2:1) gave 1.47 g (97%) of protected lactol **21** as a white solid: R_f 0.81, hexanes–ether, 1:1; IR ($CHCl_3$) 3020, 2990, 2940, 2920, 2905, 2820, 1460, 1440, 1385, 1374, 1360, 1318, 1282, 1250, 1233, 1175, 1160, 1110, 1088, 1080, 1060, 1043, 990, 960, 945, 915, 865, 860, 840 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.54 (d, 1 H, J = 7 Hz), 4.50 (dd, 1 H, J = 9, 6 Hz), 3.65 (br s, 1 H), 3.33 (s, 3 H), 3.27 (s, 3 H), 3.26 (m, 1 H), 1.66 (s, 3 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 0.83 (d, 3 H, J = 6 Hz); high-resolution MS, calcd for $C_{22}H_{36}O_3$ 348.2664, found 348.2646. An analytical sample was prepared by recrystallization from methanol, mp 127–128 °C. Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.76; H, 10.38.

(1β,9β,16β)-1,16-Dimethoxypicrasan-12-one (32). To a rapidly stirred solution of 1.5 g (4.31 mmol) of tetracyclic olefin **21** in 150 mL of anhydrous tetrahydrofuran at 0 °C under argon was added dropwise over 15 min 13.0 mL (13 mmol) of a 1.0 M solution of diborane in tetrahydrofuran. The reaction was stirred at 0 °C for 30 min and at room temperature for 2 h. The intermediate organoborane was oxidized at 0 °C by adding, successively, 12.5 mL of a 3.0 N sodium hydroxide solution and 12.5 mL of 30% hydrogen peroxide. Complete oxidation was ensured by maintaining the reaction mixture at 50 °C for 45 min. After cooling to room temperature, the reaction was saturated with sodium chloride. The organic phase was successively washed with water, 10% sodium sulfite, and brine. The aqueous phase was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo gave 1.5 g of crude alcohol as a white foam, which was used in the next reaction without purification.

To a mechanically stirred solution of 3.89 g (49.2 mmol) of dry pyridine in 150 mL of dry methylene chloride cooled to 0 °C under argon was added 2.46 g (24.6 mmol) of chromium trioxide. After 30 min at 0 °C, 12.7 g of celite was added followed by the addition of the above alcohol in 15 mL of dry methylene chloride. After an additional 30 min at 0 °C, 12.7 g of sodium bisulfate monohydrate was added and stirring was continued for 30 min at room temperature. The reaction mixture was filtered through a pad of magnesium sulfate, which was thoroughly washed with ether. The filtrate and ether washes were concentrated in vacuo. The crude product **32** was chromatographed on 25 g of silica gel. Elution with hexanes–ether, 2:1, afforded 1.34 g (86%) of tetracyclic ketone **32** as a crystalline compound: R_f 0.47, hexanes–ether, 1:1; IR ($CHCl_3$) 2990, 2943, 2925, 2908, 2890, 1700, 1458, 1440, 1368, 1230, 1180, 1135, 1092, 1080, 1050, 1030, 982, 947, 930, 885, 860 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 4.73 (d, 1 H, J = 5.5 Hz), 3.77 (m, 1 H), 3.33 (s, 3 H), 3.30 (m, 1 H), 3.27 (s, 3 H), 1.33 (s, 3 H), 1.10 (s, 3 H), 1.03 (d, 3 H, J = 6.5 Hz), 0.87 (d, 3 H, J = 6 Hz). An analytical sample was prepared by recrystallization from ether, mp 137–139 °C. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.71; H, 10.05.

(1β,9β,16β)-1,16-Dimethoxypicras-11-ene (34, R = H). A solution of 980 mg (2.69 mmol) of tetracyclic ketone **32** and 610 mg (3.28 mmol) of p-toluenesulfonhydrazide in 100 mL of absolute methanol and 20 μL of 37% hydrochloric acid was stirred at room temperature for 3 h. The solvent was removed on a rotary evaporator under reduced pressure, and the residue was taken up in 30 mL of anhydrous benzene and evaporated to dryness. This process was repeated and the resulting tosylhydrazone was dried at 0.5 mmHg for 2 h. The tosylhydrazone was dissolved in 225 mL of anhydrous tetrahydrofuran under argon and was cooled to −78 °C. To the resulting solution was added dropwise 23 mL (32.2 mmol) of a 1.4 M solution of *n*-butyllithium in hexane. The mixture was stirred 30 min at −78 °C, 2 h at 0 °C, and finally 2 h at room temperature. The reaction was quenched at 0 °C with saturated aqueous ammonium chloride. The solvent was evaporated under reduced pressure, and the

residue was taken up in methylene chloride and was washed with water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The crude product was chromatographed on 25 g of silica gel. Elution with hexanes–ether, 3:1, gave 802 mg (86%) of tetracyclic olefin **34** (R = H) as a white solid: R_f 0.67, hexanes–ether, 3:1; IR ($CHCl_3$) 3020, 2988, 2947, 2925, 2895, 2865, 2840, 2820, 1460, 1445, 1378, 1360, 1345, 1272, 1233, 1175, 1130, 1115, 1080, 1060, 1040, 995, 945, 835 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 6.13 (dt, 1 H, J = 9, 4 Hz), 5.55 (dt, 1 H, J = 9, 4 Hz), 4.35 (dd, 1 H, J = 9, 6 Hz), 3.63 (m, 1 H), 3.47 (dd, 1 H, J = 10.5, 6 Hz), 3.29 (s, 3 H), 3.20 (s, 3 H), 1.18 (s, 3 H), 1.03 (d, 3 H, J = 7.5 Hz), 1.01 (s, 3 H), 0.80 (d, 3 H, J = 6 Hz); high-resolution MS, calcd for $C_{22}H_{36}O_3$ 348.2664, found 348.2646. An analytical sample was prepared by recrystallization from methanol, mp 79–80 °C. Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.71; H, 10.39.

(1β,9β,11β,12β,16β)-11,12-Epoxy-1,16-dimethoxypicrasane (35). To a solution of 1.0 g (2.87 mmol) of tetracyclic olefin **34** (R = H) in 50 mL of methanol and 2.5 g of benzonitrile was added 375 mg of potassium bicarbonate and 1.5 g (22 mmol) of 50% hydrogen peroxide. The reaction mixture was stirred at room temperature for 48 h. The mixture was diluted with 100 mL of ether and 25 mL of water. The aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo provided a residue, which was chromatographed on 80 g of silica gel. Elution with hexanes–ether (1:1) afforded 865 mg (83%) of epoxide **35** as a crystalline material: R_f 0.33, hexanes–ether, 1:2; IR ($CHCl_3$) 2983, 2942, 2930, 2892, 2817, 1465, 1446, 1380, 1320, 1240, 1180, 1140, 1115, 1080, 1055, 1038, 995, 950, 918, 870, 850, 838 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 4.55 (dd, 1 H, J = 8, 5.5 Hz), 3.70 (m, 1 H), 3.49 (dd, 1 H, J = 10.5, 5.5 Hz), 3.40 (s, 3 H), 3.37 (s, 3 H), 3.27 (t, 1 H, J = 5.5 Hz), 2.78 (t, 1 H, J = 5.5 Hz), 1.16 (s, 3 H), 1.15 (d, 3 H, J = 7 Hz), 1.04 (s, 3 H), 0.84 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ether, mp 129–130 °C. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.65; H, 10.01.

[1S-(1α,2α,3β,4α,4aβ,4bβ,5β,8α,8aα,10α,10aβ)]-1,2,3,4,4a,4b,5,6,7,8,8a,9,10,10a-Tetradecahydro-3-hydroxy-5-methoxy-2,4b,8,10a-tetramethyl-4,10-epoxyphenanthrene-1-acetaldehyde (36, R = CHO). A solution of 26 mg (0.071 mmol) of tetracyclic epoxide **35** in 0.5 mL of acetone, 0.1 mL of water, and 50 μL of concentrated hydrochloric acid was stirred at room temperature for 2 h. The mixture was extracted with 3 × 50-mL portions of ether. The combined ether extracts were washed with brine and were dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo provided crude **36** (R = CHO), which was chromatographed on 5 g of silica gel. Elution with ether afforded 23 mg of aldehyde **36** (R = CHO) (92%) as a white crystalline solid: R_f 0.38, ether; IR ($CHCl_3$) 3590, 3410, 3020, 2990, 2940, 2930, 2870, 2840, 2816, 2715, 1715, 1458, 1450, 1435, 1380, 1370, 1350, 1335, 1305, 1290, 1280, 1255, 1235, 1172, 1122, 1090, 1065, 1030, 995, 955, 945, 935, 905, 883 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 9.85 (t, 1 H, J = 1.5 Hz), 4.10 (s, 1 H), 3.72 (d, 1 H, J = 5 Hz), 3.33 (s, 3 H), 3.17 (dd, 1 H, J = 10.5, 4.8 Hz), 2.50 (s, 1 H), 1.26 (s, 3 H), 0.98 (s, 3 H), 0.96 (d, 3 H, J = 7.2 Hz), 0.76 (d, 3 H, J = 6.6 Hz). An analytical sample was prepared by recrystallization from ether, mp 146–147 °C. Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.69; H, 10.06.

[1S-(1α,2α,3β,4α,4aβ,4bβ,5β,8α,8aα,10aβ)]-1,2,3,4,4a,4b,5,6,7,8,8a,9,10,10a-Tetradecahydro-5-methoxy-1-(2-methoxyethyl)-2,4b,8,10a-tetramethyl-4,10-epoxyphenanthren-3-ol (36, R = CH_2OMe). To a suspension of 0.5 g (13.2 mmol) of lithium aluminum hydride in 4 mL of tetrahydrofuran was added dropwise a solution of 220 mg (0.604 mmol) of tetracyclic epoxide **35** in 1 mL of tetrahydrofuran. The reaction mixture was stirred at reflux under argon for 12 h and cooled to room temperature, and the excess lithium aluminum hydride was destroyed by the careful addition of wet ether. The suspension was filtered through a pad of magnesium sulfate. The solvent was evaporated in vacuo and the crude product was chromatographed on 20 g of silica gel. Elution with hexanes–ether, 1:1, gave 132 mg (60%) of alcohol **36** (R = CH_2OMe) as a white crystalline solid: IR ($CHCl_3$) 3610, 3440, 2983, 2933, 2900, 2875, 2817, 1460, 1390, 1375, 1358, 1245, 1180, 1160, 1105, 1090, 1066, 1030, 1010, 1000, 960, 940, 910, 885, 870, 855, 830 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 4.07 (s, 1 H), 3.90 (d, 1 H, J = 6.5 Hz), 3.44 (m, 2 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 3.19 (dd, 1 H, J = 11, 6.5 Hz), 2.45 (s, 1 H), 1.24 (s, 3 H), 1.05 (d, 3 H, J = 6.5 Hz), 0.98 (s, 3 H), 0.76 (d, 3 H, J = 7 Hz). An analytical sample was prepared by recrystallization from ether, mp 163–164 °C. Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 71.98; H, 10.49.

(1β,9β,11β,12β,16β)-1,16-Dimethoxypicrasane-11,12-diol (38, R = H). A solution of 100 mg (0.287 mmol) of tetracyclic olefin **34** (R = H) in 1 mL of pyridine was treated at room temperature with a solution of 82 mg (0.322 mmol) of osmium tetroxide in 1 mL of pyridine. The dark brown mixture was stirred at room temperature. After 12 h, a solution of 150 mg of sodium bisulfite in 3.0 mL of water containing 2 mL of pyridine was added. After an additional 2 h, the resulting solution was extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, and the crude residue was chromatographed on 5 g of silica gel. Elution with hexanes–ether, 1:1, gave 96 mg (88%) of crystalline diol **38** (R = H): IR ($CHCl_3$) 3400, 2980, 2946, 2920, 2900, 2820, 1460, 1440, 1392, 1380, 1365, 1332, 1320, 1200, 1175, 1130, 1100, 1070, 1040, 1010, 985, 946, 923 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 4.72 (dd, 1 H, J = 8.5, 6 Hz), 4.25 (s, 1 H, OH), 4.06 (t, 1 H, J = 6 Hz), 3.64 (dd, 1 H, J = 11, 5 Hz), 3.49 (m, 2 H), 3.35 (s, 3 H), 3.30 (s, 3 H), 2.97 (d, 1 H, OH), 1.17 (s, 3 H), 1.07 (s, 3 H), 1.00 (d, 3 H, J = 7.5 Hz), 0.85 (d, 3 H, J = 6 Hz). An analytical sample was prepared by recrystallization from ether, mp 122–124 °C. Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.39; H, 10.12.

(1β,9β,11β,12β,16β)-12-(Acetyloxy)-1,16-dimethoxypicrasane-11,12-diol (38, R = Ac). A solution of 61 mg (0.16 mmol) of diol **38** (R = H) in 0.4 mL of pyridine and 0.2 mL of acetic anhydride was stirred at room temperature for 15 h. The reaction was quenched by the addition of 1 mL of methanol. After 1 h, the solvent was evaporated under reduced pressure and the residue was chromatographed on 3 g of silica gel. Elution with hexanes–ether, 1:1, gave 61 mg (90%) of acetate **38** (R = Ac) as a white crystalline solid: IR (CCl_4) 3450, 2970, 2950, 2920, 1730, 1462, 1450, 1445, 1368, 1247, 1180, 1135, 1080, 1045, 945, 952, 925, 905 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.02 (dd, 1 H, J = 12.5, 5.0 Hz), 4.90 (dd, 1 H, J = 5.0, 6.0 Hz), 4.15 (t, 1 H, J = 6.5 Hz), 3.90 (s, 1 H, OH), 3.58 (dd, 1 H, J = 12, 5 Hz), 3.49 (m, 1 H), 3.36 (s, 3 H), 3.27 (s, 3 H), 2.18 (s, 3 H), 1.18 (s, 3 H), 1.05 (s, 3 H), 0.85 (d, 3 H, J = 7.5 Hz), 0.83 (d, 3 H, J = 5.5 Hz). An analytical sample was prepared by recrystallization from ether, mp 164–165 °C. Anal. Calcd for $C_{24}H_{40}O_6$: C, 67.89; H, 9.50. Found: C, 67.78; H, 9.46.

(1β,9β,12β,16β)-12-(Acetyloxy)-1,16-dimethoxypicrasan-11-one (39). To a solution of 3.4 mL (42 mmol) of dry pyridine in 100 mL of dry methylene chloride cooled to 0 °C was added 2.1 g (21 mmol) of chromium trioxide. After 30 min at room temperature, 4 g of celite was added. A solution of 1.3 g (3.07 mmol) of alcohol **38** (R = Ac) in 10 mL of dry methylene chloride was added to the Collins reagent. After 30 min at room temperature, 4 g of sodium hydrogen sulfate monohydrate was added. Stirring was continued for an additional 30 min followed by filtration of the reaction mixture through a pad of magnesium sulfate. The filter pad was throughly washed with ether. The combined organic washings were concentrated in vacuo on a rotary evaporator. The crude product was chromatographed on 50 g of silica gel. Elution with hexanes–ether, 1:1, gave 1.07 g (83%) of ketone **39** as a white crystalline solid: IR ($CHCl_3$) 2975, 2950, 2930, 2900, 2880, 2830, 1750, 1730, 1468, 1460, 1445, 1374, 1255, 1230, 1220, 1200, 1140, 1095, 1060, 1032, 955, 940, 890 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 4.73 (m, 2 H), 3.97 (dd, 1 H, J = 11, 5 Hz), 3.63 (m, 1 H), 3.29 (s, 3 H), 3.06 (s, 3 H), 2.87 (s, 1 H), 2.13 (s, 3 H), 1.40 (s, 3 H), 1.05 (d, 3 H, J = 7.5 Hz), 1.04 (s, 3 H), 0.86 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ether, mp 213–215 °C. Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.49; H, 9.06.

(1β,9β,16β)-1,16-Dimethoxypicrasan-11-one (40). A solution of 300 mg (1.4 mmol) of tetracyclic keto acetate **39** in 3.0 mL of dry tetrahydrofuran was added to 450 mg (11.2 mmol) of calcium in 50 mL of anhydrous liquid ammonia. After 3 min, the reaction was quenched by the addition of 1 mL of bromobenzene. The residue obtained upon evaporation of the ammonia was treated with 20 mL of water and 100 mL of ether. The organic layer was dried over anhydrous magnesium sulfate, and the filtrate was concentration in vacuo. The crude material was purified on 20 g of silica gel. Elution with hexane–ether, 2:1, provided 184 mg (71%) of crystalline **40**, mp 119–121 °C: R_f 0.54, hexanes–ether, 1:2; IR (CCl_4) 1710 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 4.70 (m, 1 H), 4.09 (dd, 1 H, J = 10.5, 4.5 Hz), 3.62 (t, 1 H, J = 3.0 Hz), 3.29 (s, 3 H), 3.11 (s, 3 H), 2.4–2.9 (m, 3 H), 1.37 (s, 3 H), 1.00 (s, 3 H), 0.98 (d, 1 H, J = 6.5 Hz), 0.85 (d, 3 H, J = 6.0 Hz). An analytical sample was prepared by recrystallization from hexanes, mp 119–121 °C. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.61; H, 9.99.

(1β,16β)-1,16-Dimethoxypicrasan-11-one (33). To a solution of 184 mg (0.51 mmol) of tetracyclic ketone **40** in 25 mL of dimethyl sulfoxide was added 920 mg of sodium methoxide. The reaction was stirred at 50–55 °C for 1 h. The reaction was quenched by the addition of 25 mL of water. The product was isolated by extraction with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and were concentrated under reduced pressure leaving 180 mg of a residue, which was chromatographed on 20 g of silica gel. Elution with hex-

anes–ether, 5:1, gave 126 mg (68%) of pure **30** as an oil: R_f 0.63, hexanes–ether, 1:2; IR (CCl_4) 1718 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 4.91 (m, 1 H), 3.65 (m, 2 H), 3.35 (s, 3 H), 3.19 (s, 3 H), 2.79 (s, 1 H), 1.28 (s, 3 H), 1.02 (s, 3 H), 0.87 (d, 3 H, J = 6.0 Hz), 0.78 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.56; H, 10.05.

(1β,9β,12β,16β)-12-Hydroxy-1,16-dimethoxypicrasan-11-one (43). A solution of 77 mg (0.21 mmol) of tetracyclic ketone **40** in 2.0 mL of dry tetrahydrofuran was added dropwise over 5 min to a solution of lithium diisopropylamide [prepared at −78 °C from 0.22 mL (0.31 mmol) of a 1.4 M solution of *n*-butyllithium in hexane and 46 μL (0.31 mmol) of diisopropylamine] in 2.0 mL of anhydrous tetrahydrofuran. After 15 min at −78 °C and 25 min at −10 °C the reaction flask was cooled to −78 °C. Freshly prepared MoO_5·py·HMPA (120 mg, 0.31 mmol) was added all at once. After 40 min the reaction mixture was warmed to 0 °C where stirring was continued for 20 min. The reaction was quenched with 4.0 mL of water. The product was isolated by extraction with ether (3 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The residue was chromatographed on 10 g of silica gel. Elution with hexanes–ether, 1:2, gave 43 mg (58%) of α-hydroxy ketone **43**: IR ($CHCl_3$) 3585, 2990, 2960, 2946, 2930, 2900, 2867, 1716, 1462, 1453, 1442, 1376, 1368, 1217, 1128, 1049, 1024, 1002, 993, 935, 884 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 4.61 (d, 1 H, J = 5 Hz), 3.99 (dd, 1 H, J = 11.5, 5 Hz), 3.58 (m, 1 H), 3.39 (dd, 1 H, J = 8.0, 5.5 Hz), 3.33 (s, 3 H), 3.10 (s, 3 H), 2.91 (s, 1 H), 2.80 (d, 1 H, J = 5.0 Hz, OH), 1.35 (s, 3 H), 1.09 (d, 3 H, J = 7.5 Hz), 1.00 (s, 3 H), 0.84 (d, 3 H, J = 7 Hz).

(1β,16β)-1,12-16-Trimethoxypicras-12-en-11-one (44). A solution of 57 mg (0.16 mmol) of α-hydroxy ketone **43** in 2.0 mL of dry dimethyl sulfoxide containing 0.2 mL of methanol was added at room temperature to 172 mg (3.18 mmol) of freshly prepared sodium methoxide under argon. The reaction mixture was stirred at 55 °C for 30 min followed by raising of the temperature to 95 °C. After 1 h, the reaction was cooled to 10 °C and treated with 296 mg (4.67 mmol) of methyl iodide. The reaction was quenched after 15 min by the addition of 50 mL of ice water. The product was isolated by extraction with ether (3 × 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on 8.0 g of silica gel by using hexane–ether (2:1). There was obtained 48 mg (82%) of **44** as a white crystalline substance: IR ($CHCl_3$) 2991, 2930, 2900, 2830, 1688, 1645, 1461, 1440, 1390, 1375, 1362, 1340, 1296, 1265, 1254, 1243, 1225, 1194, 1185, 1164, 1132, 1120, 1112, 1100, 1080, 1051, 1036, 1004, 998, 973, 952, 928, 895, 887, 866, 848, 835, 820 cm^{-1}; NMR (220 MHz) ($CDCl_3$) δ 4.86 (br d, 1 H, J = 2.5 Hz), 3.58 (s, 4 H), 3.36 (s, 3 H), 3.20 (s, 3 H), 2.77 (dd, 1 H, J = 4, 12 Hz), 2.71 (s, 1 H), 1.73 (s, 3 H), 1.34 (s, 3 H), 1.14 (s, 3 H), 0.82 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ether; mp 150–151 °C. Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.38; H, 9.30.

(9β,16β)-16-Methoxypicras-12-en-1-one (45). To a stirred solution of 850 mg (10.8 mmol) of dry pyridine in 40 mL of dry methylene chloride under argon cooled to 0 °C was added 538 mg (5.38 mmol) of chromium trioxide. After 30 min at 0 °C, 2.78 g of celite was added followed by 300 mg (0.90 mmol) of tetracyclic alcohol **23** in 10 mL of dry methylene chloride. After 30 min at 0 °C, 2.78 g of sodium hydrogen sulfate monohydrate was added. Stirring was continued for an additional 30 min at room temperature followed by filtration of the reaction mixture through a pad of magnesium sulfate. The crude product obtained by concentration of the combined organic washings was chromatographed on 15 g of silica gel. Elution with hexanes–ether, 1:1, gave after recrystallization from ether 191 mg of tetracyclic ketone **45** (64%): mp 137–138 °C; IR ($CHCl_3$) 2990, 2950, 2880, 1690, 1457, 1433, 1370, 1220, 1192, 1175, 1055, 1040, 980, 960 cm^{-1}; NMR (220 MHz) ($CDCl_3$) δ 5.45 (d, 1 H, J = 7 Hz), 4.44 (m, 1 H), 3.64 (br s, 1 H), 3.31 (s, 3 H), 1.61 (s, 3 H), 1.16 (s, 3 H), 1.07 (s, 3 H), 1.00 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.71; H, 9.63.

(9β,16β)-2,16-Dimethoxypicras-2,12-dien-1-one (46). A solution of 150 mg (0.45 mmol) of tetracyclic ketone **45** in 4 mL of dry tetrahydrofuran was added dropwise over 5 min to a solution of lithium diisopropylamide [prepared at −78 °C from 0.37 mL (0.58 mmol) of a 1.6 M solution of *n*-butyllithium in hexane and 83 μL (0.58 mmol) of diisopropylamine] in 1.0 mL of anhydrous tetrahydrofuran. After 15 min at −78 °C and 10 min at −10 °C, 321 mg (0.90 mmol) of freshly prepared MoO_5·py·HMPA was added at once. After 2 min, the reaction was quenched with 2.0 mL of a saturated sodium sulfite solution. The reaction was diluted with 3.5 mL of water and was stirred at room temperature for 15 min. The product was isolated by extraction with ether (3 × 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. The residue was chromatographed on 10 g of silica gel. Elution with hexanes–ether, 2:1, gave 67 mg (43%) of α-hydroxy ketone **47**, which was used directly in the next reaction.

A solution of 61 mg (0.18 mmol) of α-hydroxy ketone **47** in 2.2 mL of dry dimethyl sulfoxide and 0.22 mL of methanol was added at room temperature to 192 mg (3.55 mmol) of sodium methoxide (freshly prepared) under argon. The reaction was stirred at 55 °C. After 35 min the reaction was cooled to 10 °C, and 0.33 mL (5.29 mmol) of methyl iodide was added. The reaction was quenched after 15 min by the addition of 50 mL of ice water. The product was isolated by extraction with ether (3 × 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product (61 mg) was purified on 8.0 g of silica gel. Elution with hexane–ether (1:1) gave 59 mg (93%) of pure diosphenol methyl ether **46** as a white crystalline compound: IR ($CHCl_3$) 2997, 2958, 2930, 2910, 1672, 1624, 1458, 1443, 1435, 1376, 1359, 1230, 1180, 1164, 1105, 1076, 1055, 1047, 990, 960, 840 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.50 (br s, 2 H), 4.50 (dd, 1 H, J = 5.0, 9.0 Hz), 3.68 (br s, 1 H), 3.58 (s, 3 H), 3.32 (s, 3 H), 1.62 (s, 3 H), 1.20 (s, 3 H), 1.17 (d, 3 H, J = 6.5 Hz), 1.09 (s, 3 H). An analytical sample was prepared by recrystallization from ether, mp 151–152 °C. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.07; H, 8.92.

(2α,9β,11β,16β)-2,11-Dihydroxy-16-methoxypicrasane-1,12-dione (48). To a solution of lithium diisopropylamide [prepared from 224 mg (2.22 mmol) of diisopropylamine and 1.39 mL (2.22 mmol) of *n*-butyllithium (1.6 M in hexane) in 3.0 mL of anhydrous tetrahydrofuran cooled to −78 °C] at −78 °C under argon was added dropwise 150 mg (0.43 mmol) of tetracyclic diketone **15** in 6.0 mL of dry tetrahydrofuran. The reaction mixture was stirred at −78 °C for 15 min. After an additional 45 min at 0 °C to ensure complete dienolate formation, 1.53 g (4.3 mmol) of MoO_5·py·HMPA was added at once. After 15 min, the reaction was quenched by the addition of 2.0 mL of a saturated sodium sulfite solution. The reaction mixture was diluted with 50 mL of ether and 10 mL of water. The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate in vacuo afforded a residue, which was chromatographed on 30 g of silica gel. Elution with hexanes–ether, 1:2, gave 57 mg (35%) of (2α,9β,11β,16β)-2,11-dihydroxy-16-methoxypicrasane-1,12-dione (**48**) as a white crystalline solid: mp 215–218 °C; R_f 0.25, hexane–ether, 1:3, two elutions); IR ($CHCl_3$) 3560, 3440, 2940, 2900, 2870, 2820, 1725, 1450, 1360, 1125, 1100, 1055, 1025, 975, 935, 900, 880 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$, D_2O) δ 4.93 (d, 1 H, J = 12.5 Hz), 4.77 (d, 1 H, J = 5 Hz), 3.80 (br s, 1 H), 3.73 (dd, 1 H, J = 12.5, 6.0 Hz), 3.32 (s, 3 H), 2.95 (m, 1 H), 2.36 (d, 1 H, J = 12.5 Hz), 1.18 (s, 3 H), 1.09 (s, 3 H), 1.07 (d, 3 H, J = 7.0 Hz), 0.93 (d, 3 H, J = 6.0 Hz). Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 65.98; H, 8.26. In addition approximately 16 mg (10%) of an uncharacterized mixture of isomeric bis(hydroxy ketones) was isolated.

***dl*-Neoquassin *O*-Methyl Ether (49, R = Me).** A solution of 60 mg (0.16 mmol) of (2α,9β,11β,16β)-2,11-dihydroxy-16-methoxypicrasane-1,12-dione (**48**) in 3.9 mL of dry dimethyl sulfoxide containing 0.39 mL of methanol was added at room temperature in one portion to a flask containing 346 mg (6.37 mmol) of freshly prepared sodium methoxide under argon. The reaction was warmed to 55 °C where stirring was continued for 30 min prior to raising the temperature to 95 °C. After 2 h, the reaction was cooled to 10 °C and 1.32 g (9.3 mmol) of methyl iodide was added. After 15 min the reaction was quenched by the addition of 40 mL of ice water. The product was isolated by extraction with ether (3 × 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product (60 mg) was purified on 10 g of silica gel. Elution with ether–hexanes, 3:1, provided 36 mg (57%) of racemic neoquassin *O*-methyl ether (**49**, R = Me) as a crystalline substance: mp 214–216 °C; IR ($CHCl_3$) 3000, 2947, 2930, 2890, 2830, 1690, 1680, 1630, 1455, 1448, 1437, 1385, 1373, 1354, 1296, 1270, 1260, 1204, 1180, 1128, 1096, 1068, 1048, 1012, 1000, 977, 958, 936, 911, 889, 851, 835 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.27 (d, 1 H, J = 2.5 Hz), 4.79 (br s, 1 H), 3.61 (s, 4 H), 3.57 (s, 3 H), 3.35 (s, 3 H), 3.19 (s, 1 H), 2.41 (m, 1 H), 2.29 (dd, 1 H, J = 12, 5 Hz), 1.80 (s, 3 H), 1.51 (s, 3 H), 1.09 (d, 3 H, J = 6.5 Hz), 1.03 (s, 3 H). An analytical sample was prepared by recrystallization from ether, mp 214–216 °C. Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 67.98; H, 8.10.

***dl*-Quassin (1).** A solution of 12 mg (0.029 mmol) of neoquassin *O*-methyl ether (**49**, R = Me) in 3.8 mL of 60% aqueous acetic acid was refluxed for 25 min under argon. The mixture was cooled to room temperature and the solvent was evaporated in vacuo. The residue was dissolved in 1.0 mL of dry benzene and was treated with 900 mg (0.775 mmol) of Fetizon's reagent.[28] The suspension was refluxed under argon for 2 h. The mixture was cooled to room temperature. Filtration and concentration of the filtrate under reduced pressure provided an oil, which

was chromatographed on 3 g of silica gel. Elution with ether afforded 8 mg (74%) of synthetic *dl*-quassin as a white crystalline solid. An analytical sample was prepared by recrystallization from ether: mp 189-190 °C; IR ($CHCl_3$) 3010, 2995, 2965, 2925, 2864, 1730, 1695, 1634, 1458, 1450, 1438, 1377, 1348, 1293, 1259, 1215, 1090, 1032, 980 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.28 (d, 1 H, J = 2.5 Hz), 4.26 (br s, 1 H), 3.65 (s, 3 H), 3.56 (s, 3 H), 3.00 (dd, 1 H, J = 6.5, 18 Hz), 2.98 (s, 1 H), 1.86 (s, 3 H), 1.55 (s, 3 H), 1.18 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.87; H, 7.21.

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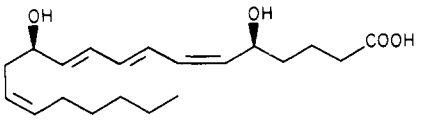
A General and Stereocontrolled Total Synthesis of Leukotriene B_4 and Analogues

K. C. Nicolaou,*† R. E. Zipkin, R. E. Dolle, and B. D. Harris

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received October 21, 1983*

Abstract: A new, general, and stereocontrolled total synthesis of leukotriene B_4 (**1**) is disclosed. The application of the methodology to the synthesis of several novel analogues of leukotriene B_4 is also described.

Leukotriene B_4 (LTB_4, **1**) is an important metabolite of the 5-lipoxygenase arachidonic acid peroxidation pathway recently isolated by incubation with polymorphonuclear leukocytes.[1]



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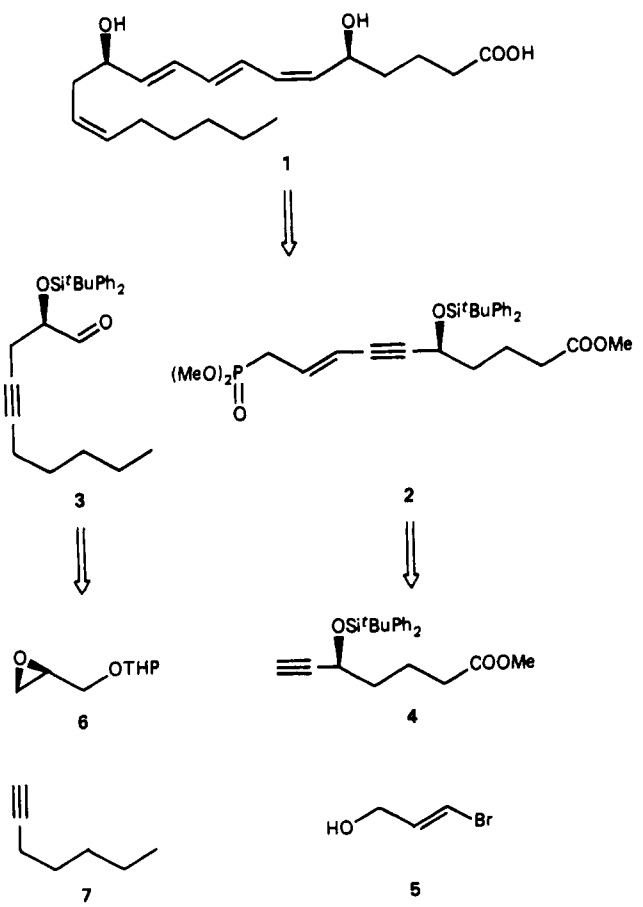
Implicated as a mediator in inflammation, this biomolecule exhibits potent chemotactic properties, facilitates adhesion of neutrophils to the endothelium, causes degranulation and release of lysosomal enzymes, increases the intracellular levels of calcium ions, and induces vascular permeability.[2] Due to its physiological importance and its low natural abundance, several syntheses of this compound have already appeared.[3-5] Despite their elegancy, however, these syntheses have limited value in the construction of certain novel analogues of LTB_4, and some of them suffer from low stereoselectivity and lengthy sequences. In this communication we wish to report a new general and efficient entry into the LTB_4 family that culminated in the total synthesis of the naturally occurring LTB_4 and of several novel structural analogues of it previously unavailable.

Scheme I outlines our retrosynthetic analysis of LTB_4, the advantages of which include (a) symmetrical disconnections leading first to two C_{10} fragments (C_1-C_{10}, **2** and C_{11}-C_{20}, **3**) and then to two C_3 fragments (**5** and **6**) and two C_7 fragments (**4** and **7**), (b) simultaneous generation of the two *Z* double bonds by controlled hydrogenation, (c) high degree of control of the geometry of the two *E* double bonds, (d) incorporation of chiral centers, and (e) flexibility to construct novel acetylenic and other LTB_4 analogues. This analysis led to a highly convergent and stereoselective strategy for the synthesis of LTB_4, the execution of which was carried out as described below.

Reaction of methyl 4-(chloroformyl)butyrate with bis(trimethylsilyl)acetylene in the presence of $AlCl_3$[6] (0 °C, CH_2Cl_2) led to the acetylenic ketone **8**[7] (60%) which was enantioselectively reduced to **9** (Scheme II) with ≥98% ee of (-)-9-pinanyl-BBN[8] (2 equiv of THF, 25 °C) in 85% chemical yield and ≥97:3 enantiomeric ratio.[9] Deprotection of the acetylene to afford **10**

Scheme I



(KF·$2H_2O$, DMF, 80%) was then followed by protection of the hydroxyl group leading to **11** (t-$BuPh_2SiCl$, imidazole, DMF,

† Fellow of the A. P. Sloan Foundation, 1979-1983, recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1984, and a J. S. Guggenheim Fellow, 1984.

(1) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643.
(2) Reviews: (a) Smith, M. J. H. *Gen. Pharmacol.* **1981**, *12*, 211. (b) Ford Hutchinson, A. W. *J. R. Soc. Med.* **1981**, *74*, 831. (c) Borgeat, P.; Sirois, P. *J. Med. Chem.* **1981**, *24*, 121. (d) Samuelsson, B. *Science (Washington, D.C.)* **1983**, *220*, 568. (e) Piper, P. J. *Trends Pharmacol. Sci.* **1983**, *4*, 75.

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