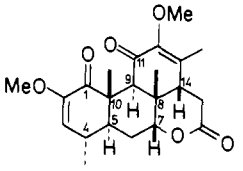
Total Synthesis of *dl*-Quassin

Sir:

During the early sixties Valenta and co-workers elucidated by classical methods the structures of quassin (**1**) and neoquassin



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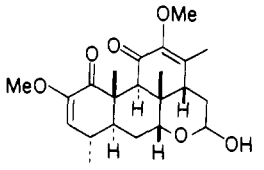

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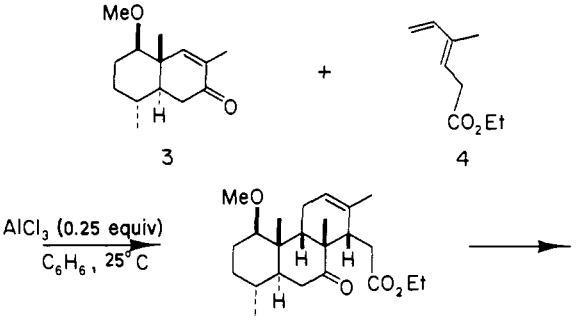
(**2**),[1] constituents of Simaroubaceae, which had first been detected in quassia wood (*Quassia amara*) in 1835.[2] Despite the recognition of the existence of bitter principles in quassia wood over a century ago, the isolation and partial purification of quassin were finally achieved in 1937 by Clark.[3] Since the recognition of the quassin structure nearly 20 years ago, extensive work has been carried out on quassinoid[4] bitter principles.[5] Much of the activity in this area has centered around the biological properties of these naturally occurring substances which possess potent antileukemic activity.[6]

The highly oxygenated tetracyclic framework of quassin coupled with its stereochemical features have stimulated a great deal of synthetic activity.[7] Despite the presence of seven chiral centers in quassin, degradative studies have established that only four of the seven centers [C(5), C(7), C(8), and C(10)] need be addressed during the preliminary synthetic planning, since the remaining three chiral centers can be generated during the final stages of the synthesis. We detail below the first total synthesis of *dl*-quassin.

A Diels-Alder strategy (cf. **3** + **4** → **5**) was employed to ensure



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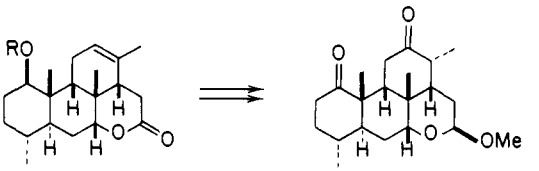
the proper stereochemistry at C(4), C(5), C(8), C(10), and C(14). The cis-fused nature of the BC rings induces hydride attack on the C(7) carbonyl from the convex face of the molecule, thereby guarantying formation of the tetracyclic lactone **6** (R = Me)



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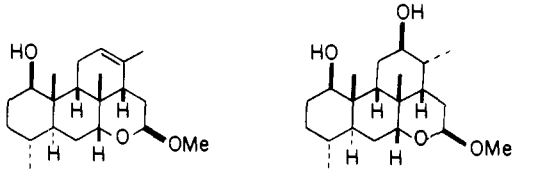
possessing the required configuration at C(7). Elaboration of **6** (R = Me) into the tetracyclic diketone **7** paves the way for simultaneous formation of the two diosphenol methyl ethers and epimerization at C(9).

The tricyclic ketone **5**, mp 87-88 °C, available from Diels-Alder reaction of enone **3** with diene **4** as previously described,[7k] was reduced with sodium borohydride in methanol giving rise to crystalline lactone **6** (R = Me),[8] mp 160-161 °C [IR ($CHCl_3$) 1738 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 5.68 (m, 1 H), 4.14 (br t, 1 H, J = 3 Hz, C(7), H), 3.28 (s, 3 H)] in 89% yield. Demethylation [$HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, HCl, 15 h] of methyl ether **6** (R = Me) by using a modification of the procedure by Fujita[9] provided the tetracyclic hydroxy lactone **6** (R = H),[8] mp 213-214 °C [IR ($CHCl_3$) 3600, 3450, 1731 cm^{-1}; ^1H NMR (90 MHz) ($CDCl_3$) δ 5.70 (br d, 1 H, J = 6 Hz), 4.19 (br t, 1 H, J = 3 Hz, C(7) H), 3.70 (t, 1 H, J = 8 Hz, C(1) H)] in 82% yield. Prior to hydroboration of the C(12)-C(13) olefinic bond, the lactone carbonyl was reduced (i-Bu_2AlH, toluene, -78 °C) and the resultant lactol was subjected to treatment with a catalytic amount of concentrated hydrochloric acid in methanol, giving rise to the protected lactol **8**,[8] mp 161-163 °C (92% overall). Hydroboration (B_2H_6, THF, 0 °C) of **8** followed by alkaline hydrogen peroxide workup yielded (77%) crystalline diol **9**,[8] mp 172-173 °C, which upon Collins oxidation generated diketone **7**,[8] mp 167-168 °C [IR ($CHCl_3$) 1705 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)] in 71% isolated yield.



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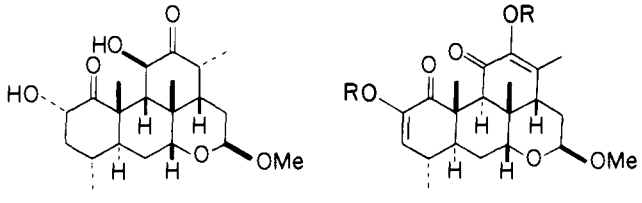
Elaboration of the diosphenol structural units was achieved via a two-step sequence. Oxygenation[10] of the dianion derived from diketone **7** [LDA (5.2 equiv), THF, -78 °C (15 min) → 0 °C (45 min); $MoO_5{\cdot}Py{\cdot}HMPA$ (10.0 equiv), 0 °C, 15 min] afforded as the major product in 35% isolated yield the crystalline bis(α-hydroxy ketone) **10**,[8,11] mp 215-218 °C [IR ($CHCl_3$) 3540, 3420, 1728 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 4.93 (d, 1 H, J =



10 11

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

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

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

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

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

(6) 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. Wall, M. E.; Wani, M. C. *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.

(7) (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. (d) *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.; Ferriño, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, 1619.

(8) All new compounds have been fully characterized, including combustion analysis.

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

(10) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(11) In addition to the major product **10**, an isomeric mixture of bis(α-hydroxy ketones) was isolated (~10%) and transformed into quassin by using the methodology described above.

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12.5 Hz, C(11) H), 4.77 (d, 1 H, J = 5 Hz, C(16) H), 3.80 (br s, 1 H, C(7) H), 3.73 (dd, 1 H, J = 12.5, 6.0 Hz, C(2) H)]. Compound **10** was smoothly transformed (50% yield) upon treatment with sodium methoxide in dimethyl sulfoxide [55 °C (30 min), 95 °C (1 h)] under argon[12] into bis(diosphenol) **11** (R = H),[8] mp 207–209 °C [IR ($CHCl_3$) 3450, 1680, 1650 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.68 (d, 1 H, J = 3 Hz, C(3) olefinic proton), 3.25 (s, 1 H, C(9) α-H), 1.84 (s, 3 H, C(13) methyl group)], possessing the desired configuration at C(9). In a subsequent step methylation (NaOMe, Me_2SO, MeI) of **11** (R = H) gave rise to **11** (R = Me),[8] mp 214–216 °C [^1H NMR (220 MHz) ($CDCl_3$) δ 3.59 (s, 3 H), 3.54 (s, 3 H), 3.34 (s, 3 H)], in 65% yield. The two-step conversion of **10** into **11** (R = Me) could be achieved in a single operation [NaOMe (40 equiv), Me_2SO–MeOH (10:1), 55 °C (30 min), 95 °C (1 h), 10 °C, MeI (15 min)] providing neoquassin β-*O*-methyl ether (**11**) (R = Me)[8] in 57% overall yield.

Selective hydrolysis [HOAc–HOH (3:2), reflux, 25 min] of the protected lactol in **11** (R = Me) afforded crystalline racemic neoquassin (**2**) identical with a sample of natural neoquassin by comparison of spectral properties [^1H NMR (220 MHz), IR] and thin-layer mobility in several solvent systems. Oxidation (Fetizon's reagent,[13] benzene, 2 h, reflux) of synthetic neoquassin provided in 77% yield from **11** (R = Me) racemic quassin, mp 189–190 °C. The overall yield of **1** from enone **3** was 2.9%. Synthetic quassin (**1**) was identical with an authentic sample by TLC, IR, and ^1H NMR (220 MHz).

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (CA 28865) from the National Cancer Institute and, in part, by G. D. Searle and Co. We are grateful to Dr. K. Kanai for experimental contributions during the very early stages of the synthesis.

(12) Attempts to carry out the transformation of **10** into **11** in an atmosphere of oxygen lead to decomposition of the intermediate diosphenols.
(13) Fetizon, M.; Golfier, M. *C. R. Acad. Sci., Ser. C* **1968**, *267*, 900.
(14) On leave from the University of Pavia, 1979–1980.

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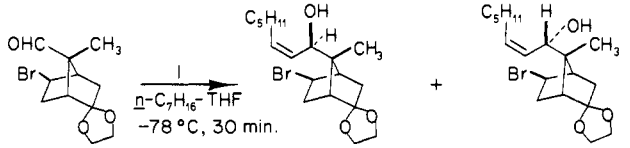
Complete Transfer of Chirality in the [3,3]-Sigmatropic Rearrangement of Allylic Acetates Catalyzed by Palladium(II). Application to Stereocontrolled Syntheses of Prostaglandins Possessing either the C-15(S) or C-15(R) Configuration

Sir:

Considerable effort has been expended during the past 10 years on the development of synthetic approaches to prostaglandins which control stereochemistry at C-15.[1] Interest in both natural and C-15 epi prostaglandins[2] has led us to devise a practical, stereocontrolled approach to prostaglandins possessing either the C-15(S) or C-15(R) configuration. We detail below the results of our investigation which addressed the question of chirality transfer in the palladium(II)-catalyzed sigmatropic rearrangement of allylic acetates.[3]

Our observation that 1-lithio-1-*cis*-heptene (**1**)[4a] adds in a highly stereoselective fashion to aldehyde **2**,[4b,6] giving rise to an 81% yield



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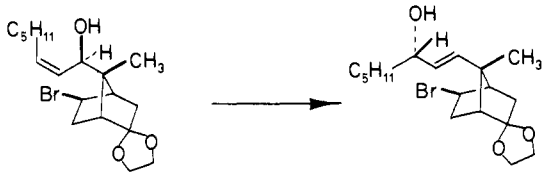
of allylic alcohol **3** [R_f 0.48 (1:1 ether–hexane)] and an 8% yield of the isomeric alcohol **4** (R_f 0.35), suggested the possibility of a stereocontrolled approach to elaboration of the ω side chain of prostanoids. Of critical importance to such a plan would be the ability to effect a complete, concerted allylic oxygen interconversion (C–O → C–O chirality transfer; cf. **3** → **5**). Although it has



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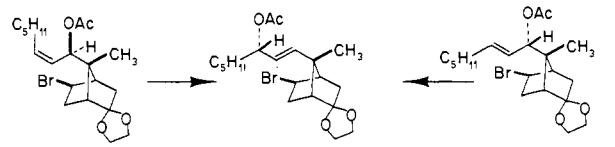
been established that catalytic amounts of palladium(II) salts will equilibrate allylic acetates,[3b] no reports dealing with transfer of chirality have appeared in the literature.[7]

Allylic alcohol **3** was converted [Ac_2O, Py, DMAP,[8] CH_2Cl_2 (96% yield)] into allylic acetate **6** and treated (25 °C) with a catalytic amount of bis(acetonitrile)palladium(II) chloride (0.04 equiv) in tetrahydrofuran for 3.5 h. *Workup provided a 91% yield of a single rearranged allylic acetate,* **7**. That **7** possessed the



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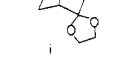
structure shown was unambiguously established by conversion[9]

(1) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491. Corey, E. J.; Becker, K. B.; Varma, R. K. *Ibid.* **1972**, *94*, 8616. Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363. Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843. Also see: Sih, J. C.; Price, P.; Sood, R.; Salomon, R. G.; Peruzzotti, G.; Casey, M. *Ibid.* **1972**, *94*, 3643. Kluge, A. F.; Untch, K. G.; Fried, J. H. *Ibid.* **1972**, *94*, 7827. Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, 2627. Bernady, K. F.; Poletto, J. F.; Weiss, M. J. *Ibid.* **1975**, 765. Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, *100*, 8271.
(2) Fried, J.; Lin, C. H. *J. Med. Chem.* **1973**, *16*, 429. Grieco, P. A.; Owens, W.; Wang, C.-L. J.; Williams, E.; Schillinger, W. J. *J. Med. Chem.* **1980**, *23*, 1072. Grieco, P. A.; Schillinger, W. J.; Yokoyama, Y. *Ibid.* **1980** *23*, 1077.
(3) (a) Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 5200. (b) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321.
(4) (a) The vinyllithium derivatives **1** and **9** were prepared by treatment of 1-iodo-1-*cis*-heptene [Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* **1967**, *89*, 5086] and 1-iodo-1-*trans*-heptene [Zweifel, G.; Whitney, C. C. *Ibid.* **1967**, *89*, 2753], respectively, with *n*-butyllithium in heptane at ~–78 °C. (b) Aldehyde **2** was prepared by Collins oxidation of the corresponding alcohol whose synthesis has been detailed on a previous occassion.[5]
(5) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.
(6) We have also observed that addition of an ethereal solution of methyl lithium to aldehyde **2** at –78 °C gave rise to an 83% isolated yield of alcohol



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i, mp 127.0–127.5 °C, whose structure was established by single-crystal X-ray analysis (unpublished results, George Majetich).
(7) Professors Eschenmoser and Overman (private communication) have independently examined the question of chirality transfer during the palladium(II)-catalyzed rearrangement of allylic acetates and have arrived at very similar conclusions.
(8) Hofle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

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