Spirocyclic Sesquiterpene Synthesis via Quinone Methide Coupling Reactions. Anhydro-β-rotunol

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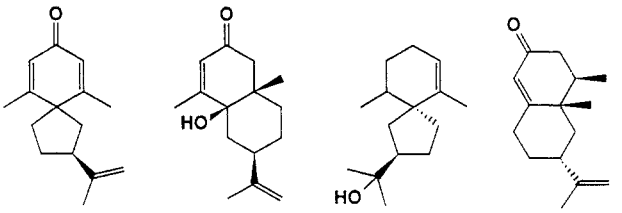
A seven-step total synthesis of **1** is reported, starting with 3,5-dimethylphenol. Formylation with $Zn(CN)_2$ gives **9**. Mesylation of the derived alcohol **10** occurs only on the phenolic OH, to give **12**. Coupling of this with the dilithium salt **15** of 2,3-dimethylbut-3-en-2-ol gives, via an unusual transmesylation reaction, followed by mesylate elimination to the reactive quinone methide intermediate **5** and trapping of this with **12**, the coupling product **21**. Hydroboration of **21** gives the triol **22**, which undergoes a regioselective dehydration and dimesylate formation, to give **25**. Base treatment of **25** causes a smooth Ar_1-5 cyclization to give **1**.

Anhydro-β-rotunol (**1**) is a stress metabolite isolated from potato tubers that have been attacked by the fungus *Phytophora infestans*.[1] A substantial synthetic challenge is presented by this molecule, since it contains a quaternary spiro center in the sterically congested environment represented by the flanking methyl groups.

This paper details the first total synthesis of racemic anhydro-β-rotunol (**1**), by a method that allows easy construction of the C–C bonds at and adjacent to the spiro center.

Three partial syntheses of anhydro-β-rotunol have been recorded. The first of these[2] involved the fortuitous acid-catalyzed rearrangement of β-rotunol (**2**) to **1** before **1** was isolated as a natural product. Another synthesis[3] involved an allylic oxidation approach from hinesol (**3**), while the third[4] involved a photochemical dienone rearrangement aproach, starting from nootkatone (**4**).



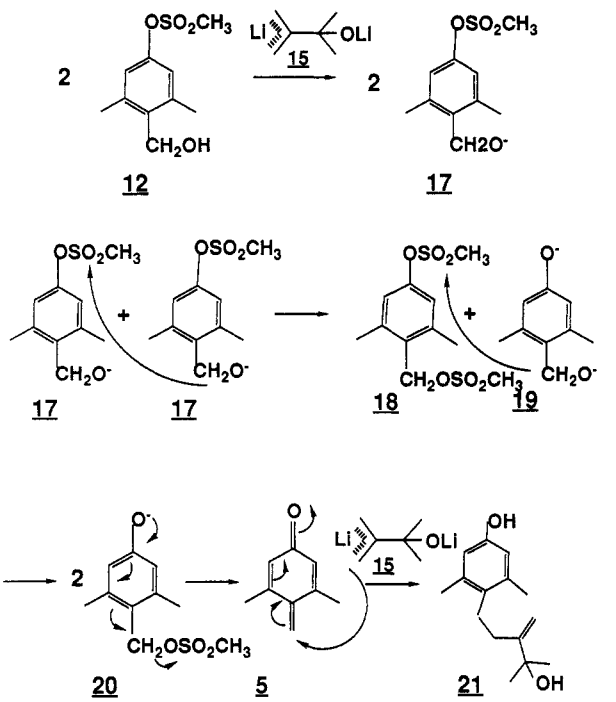
1 **2** **3** **4**

In order to overcome the steric hindrance problem, we elected to form the spirocyclic skeleton of **1** via construction of the five-membered ring onto an intact six-membered ring. We reasoned that the use of highly reactive intermediates might overcome the hindrance provided by the flanking methyl groups. An ideal precursor appeared to be the quinone methide **5**.

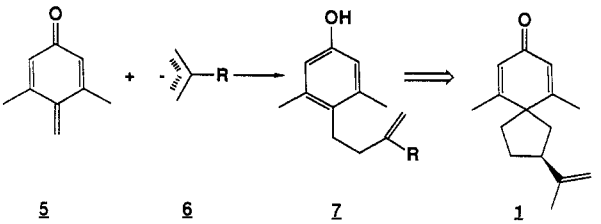
Quinone methides are highly reactive intermediates in some benzylic substitution reactions on ortho- or para-substituted phenols. Some nice examples of the use of such compounds in synthesis have been described recently.[5,6]

The key postulated step (Scheme I) in the current work was the coupling between the quinone methide **5** and a suitable carbanionic nucleophile. The choice of a 2-substituted allylic anionic species **6** allows one to capitalize upon symmetry considerations and would leave functionality (double bond) suitably placed for further manipulation in the intermediate **7**. The final spiro bond could then be produced in an intramolecular manner.

Scheme I



12 **17** **17** **17** **18** **19** **20** **5** **21**



5 **6** **7** **1**

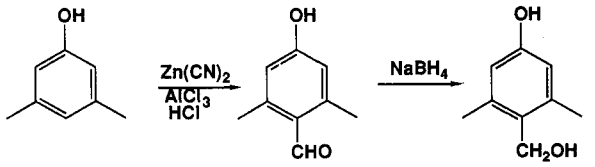
Reaction of 3,5-dimethylphenol (**8**) with HCN–$AlCl_3$–HCl in a Gatterman reaction gives the 2- and 4-formyl derivatives in about equal amounts.[7] They are separable by steam distillation.

We have found that the use of $Zn(CN)_2$ not only avoids the use of HCN but also gives the desired 4-isomer **9** (40% isolated yield), with no detectable amount of the 2-isomer. This reflects either the bulky nature of the Zn-containing complex involved in the condensation, which shields the 2-position, or else selective loss of the 2-isomer through chelation or other process. This was not investigated.

(1) Coxon, D. T.; Price, K. R.; Howard, B.; Osman, S. F.; Kalan, E. B.; Zacharias, R. M. *Tetrahedron Lett.* **1974**, 2921.
(2) Hikino, H.; Aota, K.; Kuwano, D.; Takemoto, T. *Tetrahedron Lett.* **1969**, 2741.
(3) Hikino, H.; Aota, K.; Kuwano, D.; Takemoto, T. *Tetrahedron* **1971**, *27*, 4831.
(4) Caine, D.; Chu, C.-Y. *Tetrahedron Lett.* **1974**, 703.
(5) For further examples and leading references, see: Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548.
(6) Quinone methides have also been utilized during deprotection of substituted benzyl ethers: Taylor, L. D.; Grasshoff, J. M.; and Pluhar, M. *J. Org. Chem.* **1978**, *43*, 1197.
(7) Dakshinamurty, H.; Santappa, M. *J. Org. Chem.* **1962**, *27*, 1839.

0022-3263/87/1952-0336$01.50/0

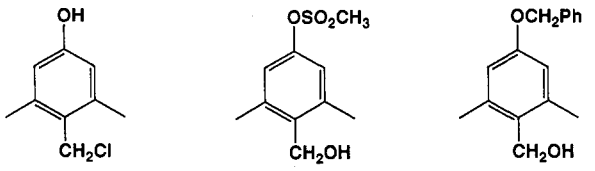
Reduction of the aldehyde in **10** with $LiAlH_4$ gave the desired alcohol, along with varying amounts of 3,4,5-trimethylphenol. This hydrogenolysis reaction may proceed through an elimination of aluminum alkoxides to give the quinone methide **5**, followed by further 1,6-reduction, though this was not investigated. In any event, reduction of the aldehyde in **9** with $NaBH_4$ was slow but gave the alcohol **10** cleanly.



8 **9** **10**

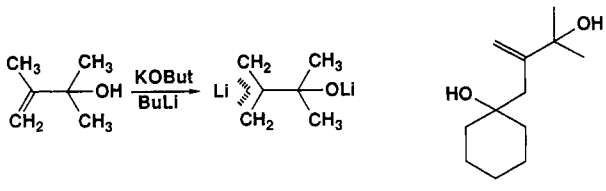
Numerous attempts were made to convert the benzylic alcohol group in **10** into a halogen leaving group as in **11**. All such attempts either gave recovered starting material or polymeric material.

Treatment of **10** with methanesulfonyl chloride and pyridine or triethylamine gave the phenol mesylate **12**. Protection of the phenol as its benzyl ether **13** and attempted mesylate formation under forcing conditions gave only recovered starting material. This clearly reflects steric hindrance at this benzylic position. Fortunately, the phenol mesylate **12** proved to be a suitable precursor for further work.



11 **12** **13**

As choice for the coupling partner **6**, the dilithium salt **15** was investigated. Direct double deprotonation of 2,3-dimethylbut-3-en-2-ol (**14**) with the complex base derived from KOBu-*t* and *n*-BuLi proved to be suitable for this reaction, similarly to the precedented case using methallyl alcohol.[8] The reagent was characterized by formation of the adduct **16** with cyclohexanone.



14 **15** **16**

Addition of the phenol mesylate **12** to a freshly prepared solution of 3.0 equiv of the dilithium reagent **15** gave the coupling product **21** in 38% yield (Scheme I). This serendipitous discovery allowed the smooth one-step construction of a precursor for anhydro-β-rotunol containing all of the requisite carbon atoms.

The mechanism postulated for this unusual coupling reaction is shown in Scheme I. Deprotonation of the phenol gives anion **17**, which attacks a second molecule of **17**, to give the dimesylate **18** and the dianion **19**. Further attack by **19** on **18** then gives two molecules of the desired phenoxide **20**, which then eliminates mesylate to give the desired quinone methide. Trapping of this with the dilithium salt **15** gives the desired coupling product **21** after workup.

The following experimental facts are in accord with this mechanism: (a) Substitution of the diol **10** for the mesylate **12** gave only recovered starting diol **10**. (b) Treatment of the dilithium salt **15** with diol **10** and methanesulfonyl chloride gave only recovered diol. Presumably, the more reactive methanesulfonyl chloride reacted only with excess *tert*-butoxide in the system. (c) Use of phenyl mesylate with the diol **12** and the dilithium derivative **15** did give a small yield (ca. 5%) of the coupling product **21**.[9]

Functionalization of the double bond in **21** could be effected by simple hydroboration with $BH_3{\cdot}SMe_2$ followed by H_2O_2 in NaOH, to give the triol **22** as the only product (99%). No oxidation of the phenol group was observed.

Even though the primary alcohol group in **22** is not nearly as sterically hindered as the one in **12**, it was not possible to form a mesylate at that position selectively. Treatment of the triol **22** with 1 equiv of methanesulfonyl chloride in pyridine or triethylamine formed the monomesylate **23** selectively. However, prolonged treatment of the triol **22** or the mesylate **23** with excess of methanesulfonyl chloride in pyridine gave selective dehydration of the tertiary alcohol to give exclusively the isopropenyl compound **24**. This selective Hoffman-type dehydration is best explained by neighboring-group participation, as shown in Scheme I.

Since mesylation of triol **22** gave selective monomesylation on the phenol group, it appeared necessary to protect the phenol. This could be done cleanly with a benzyl group. However, a better solution to the problem was at hand, by using the mesylate itself as a protecting group.

Treatment of triol **22** or either of the compounds **23** or **24** with excess methanesulfonyl chloride in pyridine gave, after 5 days at 25 °C, the dehydrated dimesylate **25** as the only recognizable organic-soluble product (27% yield), which could be purified readily.

Treatment of dimesylate **25** with KOBu-*t* in *t*-BuOH effected a smooth demesylation of the phenolic position, followed by an Ar_1–5 substitution,[10] to close the spirocyclic ring. Anhydro-β-rotunol was the only product from this reaction.

No authentic sample of anhydro-β-rotunol could be located, but the detailed NMR and IR spectra were identical with authentic spectra.[11] The compound showed one peak by VPC (none of the isomeric isopropylidine compound **3** was detected), and the mass spectrum was consistent with the structure.

The use of aromatic sulfonate esters as selective sulfonate transfer agents may have more general use. This is under investigation in this laboratory.

Experimental Section

General. General workup of reactions was carried out by the addition of water, neutralization as appropriate with 5% HCl or $NaHCO_3$, several extractions with ether, drying over $MgSO_4$, filtration, and removal of solvent with a Büchi Rotavapor. Final drying and/or removal of solvents on some small-scale reactions was done with a vacuum pump at 0.1–0.3 mmHg.

Column chromatography was carried out by packing a glass column with a 60–200-mesh silica gel (Sargent-Welch) in the apropriate solvent—usually a mixture of petroleum ether (distilled, bp 30–60 °C) and ether—and eluting with increasing ratios of

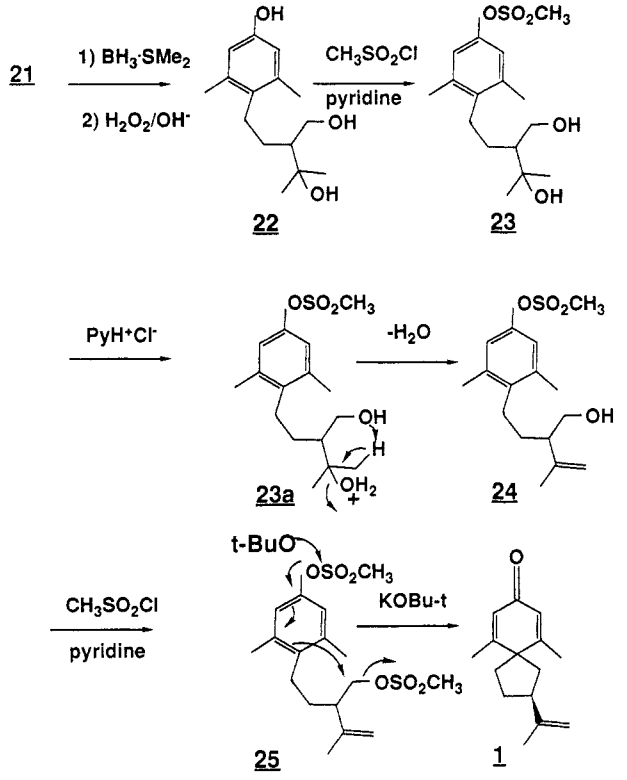
(8) Carlson, R. M.; *Tetrahedron Lett.* **1978**, 111. Gavdillo, G.; Contento, M.; Sandri, S.; Panuzio, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1729.

(9) We thank Sammy Rivas for this result.

(10) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756. Masamune, S. *J. Am. Chem. Soc.* **1961**, *83*, 1009.

(11) Copies of spectra were generously supplied by Drury S. Caine, David T. Coxon, and H. Hikano.

Scheme II



ether. All NMR spectra were run on a Varian EM-360 (60 MHz) or a Varian XL-100 (100 MHz) spectrometer in $CDCl_3$ or Me_2SO-d_6 solution with Me_4Si for internal reference.

Infrared spectra were obtained with a Nicolet FT-IR spectrometer in KBr pellets or as thin films on NaCl plates.

Elemental analyses were carried out by Atlantic Microlab, Atlanta, GA.

2,6-Dimethyl-4-hydroxybenzaldehyde (9). To a solution containing 15.0 g of 3,5-dimethylphenol in 60 mL of dry benzene was passed dry HCl for a few minutes. Then 28.76 g of powdered zinc cyanide was added slowly with vigorous stirring. Dry HCl was passed through the solution for 1 h further at 25 °C, during which a yellowish precipitate formed. The mixture was cooled in an ice bath, and 24.5 g of powdered anhydrous $AlCl_3$ was added slowly. Then the ice bath was removed and dry HCl was kept passing through the mixture for 4 h at 40–45 °C. The mixture, containing a purple precipitate, was cooled to 0 °C, and 300 mL of distilled water was added cautiously, followed by 90 mL of 10% HCl solution. After the mixture was stirred for 1 h, the yellow precipitate was filtered, the benzene layer was removed, and the aqueous layer was extracted several times with ether. The ether extract and the solid were combined to give 7.10 g of crude product (40% yield). Purification by column chromatography with 10% ether–90% petroleum ether elution provided pure colorless needles: mp 190–193 °C (lit.[8] mp 190 °C); NMR (Me_2SO-d_6) δ 10.34 (s, 1 H), 6.52 (s, 2 H), 2.50 (s, 6 H); IR (KBr) 3165 (s, OH), 2980 (s, CH), 1653 (s, C=O), 1599 (s, C=C) cm^{-1}.

2,6-Dimethyl-4-hydroxybenzyl Alcohol (10). A solution of $NaBH_4$ (3.15 g) in 95 mL of 95% EtOH was added dropwise with stirring during 1 h to a solution of 5.0 g of **9** in 85 mL of 95% EtOH. Stirring was continued for 4 h at 0 °C and then overnight at 25 °C. After removal of solvent, 60 mL of H_2O was added, followed by 10% H_2SO_4 to pH 2. After the mixture was stirred for 1 h, it was extracted several times with ether, to give 4.65 g of a yellow product (92% yield). Recrystallization from ethyl acetate gave white crystals: mp 155–159 °C; NMR (Me_2SO-d_6) δ 9.03 (s, 1 H), 6.38 (s, 2 H), 4.68 (s, 1 H), 4.38 (s, 2 H), 2.21 (s, 6 H); IR (KBr) 3410, 3103 (s, OH), 2980 (s, CH), 1599 (s, C=C), 1206 (m, CO) cm^{-1}. Anal. Calcd for $C_9H_{12}O_2$: C, 72.03; H, 7.95. Found: C, 72.89; H, 7.98.

3,5-Dimethyl-4-(hydroxymethyl)phenyl Methanesulfonate (12). To a solution of 5.0 g of **10** in 60 mL of dry THF was added 3.64 mL of $MeSO_2Cl$ with stirring. Then 13 mL of triethylamine was added dropwise. The mixture was stirred for 2 days, and then $Et_3N \cdot HCl$ was removed by filtration. The solvent was removed and the residue chromatographed on silica gel with 20% ether–80% petroleum ether to give 1.77 g (23% yield) of **12** as white needles: mp 88–90 °C; NMR ($CDCl_3$) δ 6.93 (s, 2 H), 4.60 (s, 2 H), 3.22 (s, 3 H and 1 H), 2.43 (s, 6 H); IR (KBr) 3410 (w, OH), 2933 (m, CH), 1597 (m, C=C), 1357, 1172 (s, OSO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13; S, 13.92. Found: C, 52.32; H, 6.04; S, 14.08.

5-(2,6-Dimethyl-4-hydroxyphenyl)-3-methylidene-2-methyl-2-pentanol (21). To a suspension of 2.78 g of KOBu-*t* in 25 mL of hexane in an ice bath under N_2 with stirring was added 1.17 g of 2,3-dimethyl-3-buten-2-ol (ICN) by syringe, followed by 11.4 mL of 2.0 M *n*-butyllithium over a 15-min period. To the golden suspension was added rapidly 0.90 g of **12** with vigorous stirring. The mixture was stirred for 2 h at 0 °C and for 48 h at 25 °C. Then 40 mL of H_2O was added and stirring continued for 30 min. The solution was acidified with 10% HCl and then extracted with ether. The residue was chromatographed on silica gel. Elution with 30% ether–70% petroleum ether gave 0.38 g (38% yield) of **21** as white needles: mp 114–117 °C; NMR δ ($CDCl_3$) 6.53 (s, 2 H), 5.23 (s, 1 H), 4.96 (s, 1 H), 3.2–2.6 (m, 6 H), 2.23 (s, 6 H), 1.34 (s, 6 H); IR (KBr) 3421, 3200 (s, OH), 2970 (ms, CH), 1601 (s, C=C), 1143 (s, CO), 893 (s, $C=CH_2$). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.84; H, 9.33.

5-(2,6-Dimethyl-4-hydroxyphenyl)-3-(hydroxymethyl)-2-methyl-2-pentanol (22). To a solution of 0.20 g of **21** in 20 mL of dry THF under N_2 at 0 °C was added 0.86 mL of borane–methyl sulfide slowly via syringe. The solution was stirred for 1 h at 0 °C, for 5 h at 25 °C, and at reflux for 2 h. The solution was cooled, and 0.16 mL of H_2O was added slowly, followed by 0.36 mL of 3 N NaOH. The mixture was kept in an ice bath, while 0.24 mL of 30% H_2O_2 was added. The mixture was allowed to warm and then refluxed for 2 h. The solvent was removed and the residue acidified and extracted with ether to give 0.212 g (99% yield) of **22** as a yellowish oil: NMR ($CDCl_3$) δ 6.50 (s, 2 H), 4.45–3.45 (m, 4 H), 2.80–2.35 (m, 3 H), 2.17 (s, 7 H), 1.90–1.60 (m, 2 H), 1.27 (s, 3 H), 1.10 (s, 3 H); IR (film) 3381 (s, OH), 2980 (s, CH), 1599 (m, C=C), 1141 (m, CO), 1028 (m, CO) cm^{-1}.

4-[2,6-Dimethyl-4-[(methylsulfonyl)oxy]phenyl]-2-isopropenylbutyl Methanesulfonate (25). To a solution containing 40 mg of **22** in 5 mL of dry pyridine was added 4 mL of $MeSO_2Cl$. After the mixture was stirred for 5 days at room temperature, a black precipitate was removed by filtration. The filtrate was poured into ice–water and extracted with ether. The residue was chromatographed on silica gel with 80% ether–20% petroleum ether to give 15 mg (27% yield) of **25** as a yellowish oil: NMR ($CDCl_3$, 100 MHz) δ 6.90 (s, 2 H), 5.01 (s, 1 H), 4.91 (s, 1 H), 4.22 (s, 1 H), 4.16 (s, 1 H), 3.12 (s, 4 H), 3.00 (s, 4 H), 2.80–2.40 (m, 3 H), 2.30 (s, 6 H), 1.80 (s, 3 H); IR (film) 2943 (m, CH), 1595 (m, C=C), 1359, 1174 (s, OSO_2) cm^{-1}.

Anhydro-β-rotunol (1). To a solution of 10 mg of **25** in 10 mL of dry *tert*-butyl alcohol under N_2 was added rapidly an excess of KOBu-*t* (30–40 mg). The mixture was refluxed for 6 h and then cooled, and then 3 mL of H_2O was added. After acidification with 10% HCl and ether extraction, the residue was chromatographed on silica gel with 70% ether–30% petroleum ether to give **1** as a slightly yellowish oil. The NMR and IR spectra of the product matched with the spectral data of anhydro-β-rotunol supplied by the other workers:[11] NMR ($CDCl_3$, 100 MHz) δ 6.01 (s, 2 H), 4.78 (s, 2 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 1.80 (s, 3 H), 1.79 (s, 3 H); IR (film) 1662, 1606 (s, dienone), 887 (s, vinylidene) cm^{-1} (Coxon et al.[1] give 1666, 1620, 1606, and 892 cm^{-1}); UV (EtOH) λ_{max} 243.5 nm (lit.[1] λ_{max} (EtOH) 243 nm). In addition, VPC analysis showed only one major peak and indicated >99% purity. The mass spectrum of **1** showed m/e ($M^{+\cdot}$ = 216).

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Registry No. (±)-**1**, 55869-80-2; **8**, 108-68-9; **9**, 70547-87-4; **10**, 28636-93-3; **12**, 105970-33-0; **21**, 105970-34-1; (±)-**22**, 105970-35-2; (±)-**25**, 105970-36-3; 2,3-dimethyl-3-buten-2-ol, 10473-13-9.