Stereoselective Synthesis of Racemic Trichodiene

Summary: Lewis acid induced combination of 2-[(phenylthio)methyl]-1,3-butadiene (**8**) and the α-methylene lactone **4** stereoselectively yields the adduct **9** which was converted into the sesquiterpene hydrocarbon trichodiene (**1**).

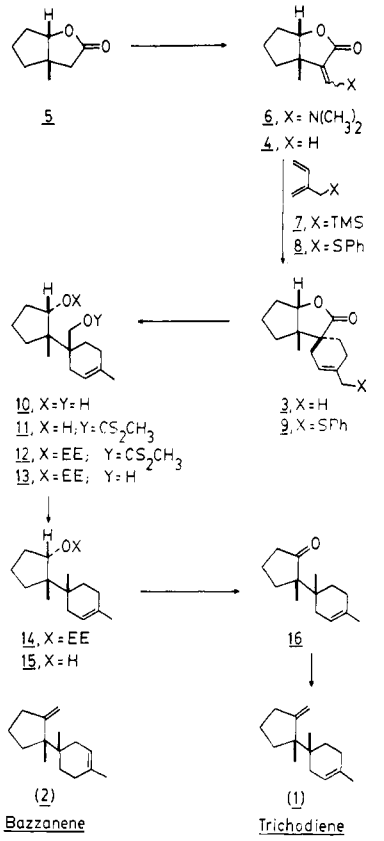
Sir: Trichothecenes are a group of mycotoxins[1] of which trichodiene (**1**) is the parent hydrocarbon.[2] Currently, there is considerable interest in the biosynthetic origin of trichodiene from farnesyl pyrophosphate;[3] however, these studies have been restricted by the low yields of trichodiene obtainable from the organism *Trichothecim roseum*. In view of this problem, we undertook development of an efficient and stereoselective synthesis of **1**.[4]

A survey of the existing synthetic literature on trichodiene indicated that several interesting syntheses of the hydrocarbon **1** had been carried out. However, with one exception,[5] these efforts led to the production of both trichodiene and its companion hydrocarbon bazzanene (**2**), substances which according to the literature can be separated only by chromatography on silver nitrate impregnated silica gel.[6]

Our thinking regarding a construction of trichodiene led us to reformulate the natural product as the tricyclic lactone **3**, a substance potentially derivable from the α-methylene lactone **4** and isoprene. Critical to the success of this strategy was the requirement that the Diels–Alder reaction be both regio- and stereoselective (e.g., reaction at the convex face of **4** with para orientation of the diene component relative to the dienophile). We describe here the application of this scenario to the formation of trichodiene.

To secure the α-methylene lactone **4**, we started from the readily available bicyclic lactone **5** (prepared from cyclopentanone in four steps in 30% overall yield).[7] Introduction of the α-methylene function onto **5** was accomplished using a scheme which had been previously reported by Ziegler and Fang in their elegantly crafted syntheses of the pseudoquaianolides aromatin and confertin.[8] Thus, treatment of **5** (7.8 mmol) with neat Brederick's reagent[9] [$[(CH_3)_2N]_2CHO$-*t*-Bu; 2.6 mL, 1.57 equiv] followed by heating to 80 °C for 36 h gave after evaporation of the volatiles and vacuum chromatography (silica gel; hexane/ethyl acetate, 1:1) the vinylogous carbamate **6** in 98% yield (Scheme I). Compound **6** was then reduced by addition of it (1 equiv) to a mixture of NH_3/THF (1:1) containing lithium metal (5 equiv) and *tert*-butyl alcohol (0.8 equiv) at −78 °C followed by stirring for 30 min. The reaction was quenched with NH_4Cl, the NH_3 evaporated, and the mixture worked up in the standard manner to give the corresponding amine–lactone in 93% yield. This crude amine–lactone was then reacted with methyl iodide in refluxing methylene chloride for 2 h followed by evaporation of the solvent and excess methyl iodide. Treatment of the resulting quaternary amine salt with triethylamine (5 equiv) in dichloroethane at 65 °C for 24 h, a standard workup, and distillation of the residue at 0.3 torr gave the α-methylene lactone **4**: bp 67 °C; 62% yield; 56% overall yield from the lactone **5**.

Scheme I



Initially, we examined the thermal combination of isoprene and **4** and were disappointed to find that a mixture of two Diels–Alder adducts in a ratio of 3:1 (para to meta diene orientation) was formed. These materials could be only partially separated by tedious chromatography. Enhancement of this ratio of adducts by use of Lewis acids was to no avail.[10] We then explored the use of 2-[(trimethylsilyl)methyl]-1,3-butadiene (**7**)[11] in combination

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(4) We thank Professor Cane (Brown University) for pointing out the relative rarity of trichodiene and for suggesting to us that a stereoselective construction of this molecule would be worthwhile.

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(6) (a) Suda, M. *Tetrahedron Lett.* **1982**, *23*, 427 and references cited therein. (b) Yamakawa, K.; Sakaguchi, R.; Nakanura, T.; Watanabe, K. *Chem. Lett.* **1976**, 991. These authors prepared ketone **16** which is a formal total synthesis of trichodiene.

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with 4 using Et_2AlCl as the Lewis acid catalyst. This reaction resulted in a 90% yield of adducts formed in a ratio of 95:5 (para to meta); however, protodesilylation of these adducts resulted in an inseparable mixture of endo and exo cyclic olefins under a variety of conditions.

While disappointing, the reaction of **7** and **4** suggested to us that a combination of the α-methylene lactone and an isoprene unit suitably functionalized with a heteroatom on the methyl group would result in stereoselective formation of the required Diels–Alder adduct. To this end, we then prepared 2-[(phenylthio)methyl]-1,3-butadiene (**8**) by reaction of 3-(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide[12] with the sodium salt of thiophenoxide followed by cheletropic elimination of sulfur dioxide.[13] Reaction of **8** (3 equiv) with the methylene lactone **4** (1 equiv) in benzene (1 M) containing Et_2AlCl (0.95 equiv) at 60 °C for 14 h afforded after workup, chromatography (silica gel; hexane/ether, 4:1), and crystallization from ether and adduct **9**: mp 90.5–92 °C; 89% yield. A small amount of the adduct resulting from meta addition of the diene was also isolated from this reaction (mp 82.5–83 °C; mixture melting point with **9** of 63–79 °C). Spectroscopic analysis of **9** was completely consistent with its suggested structure and later confirmed by its conversion into trichodiene.[14]

The lactone and thiophenyl residues, having facilitated stereoselective spiroannulation of the cyclohexene ring, via the Diels–Alder reaction, were then removed by a two-stage one-pot reduction sequence. Hence, adduct **9** (1 equiv) was added in THF to a solution of lithium metal (10 equiv) in refluxing NH_3 (0.5 M), the reaction was stirred for 30 min, and the NH_3 and THF were then removed under vacuum. To the residue thus obtained was added Et_2O (0.5 M) followed by excess $LiAlH_4$, and the resulting mixture was stirred at reflux for 24 h. A standard workup gave the diol **10** as a white solid in 99% yield. Although this material was used without further purification, it could be crystallized from benzene to give white needles, mp 115–116 °C.

Required for the conversion of **10** into trichodiene was the reductive removal of the primary hydroxyl group together with transformation of the secondary hydroxyl function into an *exo*-methylene residue. Both alcohols are neopentyl in nature with a common carbon–carbon single bond between them. Thus, it was not unanticipated that attempts to distinguish these alcohols might likely lead to the formation of a tetrahydrofuran ring, a result viewed as an experimental impass. Indeed, a variety of means to secure this unwanted outcome were discovered before a reasonable method of differentiating these alcohols was revealed.

Treatment of **10** (0.2 M) in DMF at 22 °C for 15 min with a mixture of DBN (4 equiv), excess carbon disulfide, and excess methyl iodide gave the thiocarbonate **11** after workup and vacuum chromatography (silica gel; hexane/ether, 8:1).[15] The secondary alcohol was then protected by using ethyl vinyl ether (2 equiv) in methylene chloride containing PPTS to give compound **12**.[16] Reduction of crude **12** with lithium aluminum hydride (3 equiv) in THF (0.25 M) at 0 °C followed by workup and vacuum chromatography (silica gel; hexane/ether, 8:1) afforded the alcohol ether **13** in 73% overall yield from the diol **10**.[17] The primary alcohol was then removed by reaction of its lithium salt (generated by using LDA in THF) with an excess of bis(dimethylamino)phosphorochloridate followed by reductive cleavage of this residue with lithium and ethylamine containing *tert*-butyl alcohol at 0 °C.[18] Chromatography of the oil obtained from these two steps (silica gel; hexane/ether, 3:1) gave the ether **14** in 91.5% yield from **13**.

The transformation of **14** into trichodiene was initiated by hydrolysis of the ether protecting group in methanol (0.5 M) with PPTS (0.5 equiv) at 22 °C for 14 h.[16] Pyridinium chlorochromate oxidation of the crude alcohol **15** in methylene chloride (0.5 M) for 1.5 h at 22 °C followed by a standard workup and chromatography (silica gel; hexane/ether, 4:1) gave the cyclopentanone **16** in 85.5% yield from the ether **14**.[19] Wittig elaboration of **16** into trichodiene in 51% yield has been reported by Welch and co-workers, and, indeed, this result was obtained in our hands.[5] However, if this same reaction was carried out in a carefully degassed sealed tube for 60 h at 80 °C, a 75% yield of pure trichodiene could be obtained after chromatography (silica gel, hexane).[20] Thus, trichodiene (**1**) has been stereoselectively assembled in 13 steps from the lactone **5** in 21% overall yield. This synthesis permitted us to readily prepare 1 g of the sesquiterpene for use in further biosynthetic studies to be carried out by Professor David Cane.

Acknowledgment. We thank the National Institutes of Health for support of this work (Grant No. CA 28544-02).

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(13) The reaction was carried out at 180 °C (0.005 torr). The diene **8** was obtained in 90% yield upon redistillation [bp 86 °C (0.3 torr)].

(14) Satisfactory spectral and physical data were obtained for all new compounds.

(15) For an example of this reaction which distinguishes between primary and secondary alcohols, see: Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.

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(17) The use of $(Bu)_3SnH$ to reduce compound **12** directly into compound **14** gave only the corresponding tetrahydrofuran. For an example of deoxygenation of alcohols via their thiocarbonates with $(Bu)_3SnH$, see: Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

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(20) Infrared and mass spectra data for synthetic trichodiene, determined at the University of Rochester, were identical with published data for naturally occurring trichodiene. ^1H and ^{13}C spectra of synthetic trichodiene were directly compared to the natural product at Brown University by Professor Cane.

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Received November 1, 1982