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THERMAL REARRANGEMENT OF DIVINYLCYCLOPROPANE SYSTEMS.
A NEW FORMAL TOTAL SYNTHESIS OF (±)-QUADRONE

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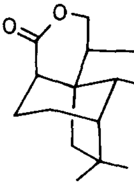
ABSTRACT: The key step of a new approach to the total synthesis of the structurally and physiologically interesting sesquiterpenoid (±)-quadrone (**1**) involves thermal (Cope) rearrangement of the highly functionalized divinylcyclopropane derivative **8**. The product **9** of this process is converted into **19**, thus completing a formal total synthesis of (±)-**1**.

(-)-Quadrone, a cytotoxic sesquiterpenoid isolated from the fungus Aspergillus terreus,[1] has been shown to possess the constitution[1a] and absolution configuration[2] shown in **1**. Over the past few years, this novel substance has been the target of much synthetic inventiveness[3,4] and a number of ingeniously designed total syntheses of (±)-quadrone have been reported.[3] We describe herein a new formal total synthesis of (±)-**1** via a route distinctly different from those reported previously.



1

The synthetic sequence employed is outlined in **Scheme 1**. The keto ketal **2**,[5] which was obtained readily from the corresponding dione,[6] was converted efficiently into the alkene **3** by means of a slightly modified Shapiro reaction.[7] Epoxidation of **3** via the corresponding bromohydrins,[8] treatment of the resultant mixture of epoxides (α-epoxide predominant) with sodium phenylselenide, and subsequent selenoxide thermolysis[9] gave a mixture of allylic alcohols which were separated by chromatography. Conversion of the major alcohol into the tert-butyldimethylsilyl ether **4** was accomplished by means of a standard procedure.

Treatment of compound **4** with ethyl diazoacetate in the presence of rhodium(II) acetate[10] provided, in excellent yield, a mixture of epimeric cyclopropanecarboxylic acid esters **5**, along with a small amount (<5%) of product resulting from carbenoid insertion into the allylic bridgehead C-H bond. From a stereochemical point of view, cyclopropanation of the alkene **4** would be expected to occur from the convex side of the molecule opposite to the silyl ether moiety, and, thus, the relative configuration of **5** could be predicted with confidence.

Subjection of the mixture of esters **5** to a reduction-oxidation sequence, followed by base-promoted equilibration of the resultant mixture of aldehydes, afforded a single substance **6**, which was converted via standard reactions into the keto alkene **7** (65% overall yield from **5**). Transformation of the ketone **7** into the enol silyl ether 8[11] set the stage for the key step of the overall synthesis, involving thermal (Cope) rearrangement of the highly functionalized divinylcyclopropane system present in 8.[12,13] Thus, thermolysis of 8 and subsequent treatment of the product 9 with tetra-*n*-butylammonium fluoride afforded, after chromatographic purification, the pure crystalline keto ketal 10 (77% from 8).

With the basic carbon framework of (±)-quadrone assembled, the functionality present in 10 had to be employed to introduce the necessary appendages. The geminal methyl groups were added by subjection of 10 to two successive treatments with lithium diisopropylamide and methyl iodide. Attempted Wolff-Kishner reduction of the resultant product 11 failed to produce the desired product 16, and, therefore, a more circuitous route for removal of the very hindered carbonyl group had to be employed. Reduction of 11 with lithium aluminum hydride produced the alcohols 12 and 13 (3:1, respectively),[14] which were converted smoothly into the corresponding phosphorodiamidates 14 and 15.[15] Unfortunately, although lithium-ethylamine reduction[15] of this mixture removed the $OPO(NMe_2)_2$ functions, substantial amounts of carbon-carbon double bond reduction also occurred. It was observed, however, that the phosphorodiamidate function of the minor epimer 15 was reductively removed much more slowly than the corresponding moiety of 14. Therefore, it appeared that the carbon-carbon double bond reduction could be largely avoided if the reduction were to be carried out on epimerically pure 14.

Treatment of 11 with lithium diisobutyl-*n*-butylaluminum hydride[16] in ether gave exclusively (>95% yield) the alcohol 12. Reduction of the corresponding phosphorodiamidate 14 with lithium in methylamine[17] provided mainly the desired alkene 16, accompanied by a minor amount (~10%) of the over-reduced product.

Epoxidation of 16 occurred exclusively from the less hindered β-face of the molecule. Treatment of the resultant epoxide with lithium diethylamide in benzene[18] gave, after chromatographic purification of the crude product, the pure allylic alcohol 17. This material differs only in the nature of the ketal protecting group from an intermediate employed by Burke and coworkers[3c] in their synthesis of (±)-quadrone. Indeed, the 4-step sequence which we employed to convert 17 into 19 was, except for the third step, essentially identical with that reported previously by Burke *et al.*[3c] Thus, conversion of the alcohol 17 into the corresponding vinyl ether, followed by Claisen rearrangement of the latter substance, gave the olefinic aldehyde 18. Hydrogenation of 18 in hexane[19] and subsequent removal of the ketal protecting group provided the keto aldehyde 19,[20] which had been converted previously into (±)-quadrone.[3c]

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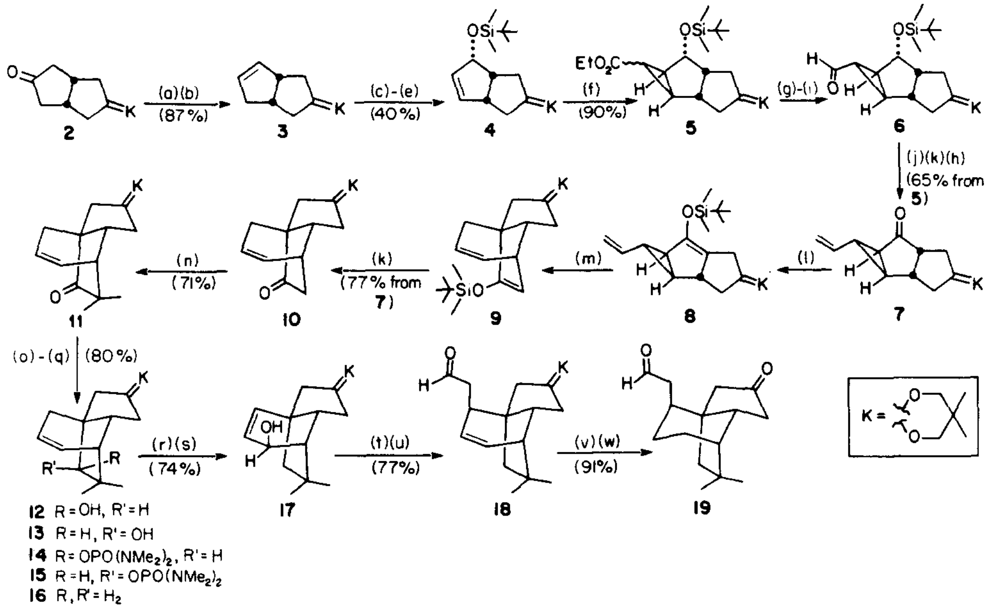

Scheme 1. (a) p-TsNHNH$_2$, EtOH (b) n-BuLi, Et$_2$O-HMPA (c) NBS, DMSO-H$_2$O; K$_2$CO$_3$, MeOH (d) PhSeNa, EtOH-THF; H$_2$O$_2$-H$_2$O, heat (e) t-BuMe$_2$SiCl, imidazole, DMF (f) N$_2$CHCO$_2$Et, Rh$_2$(OAc)$_4$ (g) LiAlH$_4$, Et$_2$O (h) C$_5$H$_5$N·CrO$_3$·HCl, NaOAc, CH$_2$Cl$_2$ (i) t-BuOK, t-BuOH-THF (j) Ph$_3$P = CH$_2$, THF (k) n-Bu$_4$NF, THF (l) LDA, THF, -78°C; t-BuMe$_2$SiOTf, THF-HMPA (m) 170-175°C, 5 h, C$_6$H$_6$ (sealed tube) (n) LDA, THF; MeI (2 times) (o) Li(n-Bu)(i-Bu)$_2$AlH, Et$_2$O (p) n-BuLi, THF; ClPO(NMe$_2$)$_2$, THF-HMPA (q) Li, MeNH$_2$, -20°C, 10 min (r) m-Chloroperoxybenzoic acid, CH$_2$Cl$_2$ (s) LiNEt$_2$, C$_6$H$_6$, reflux (t) EtOCH=CH$_2$, Hg(OAc)$_2$ (u) 240°C, 4.5 h, C$_6$H$_6$ (sealed tube) (v) H$_2$, 10% Pd-on-C, hexane (w) HCl, H$_2$O, acetone.

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5 All compounds reported herein exhibited spectra in accord with structural assignments and gave satisfactory high resolution mass spectrometric molecular mass determinations and/or elemental analyses.

6 Kubiak, G.; Cook, J.M.; Weiss, U. *J. Org. Chem.* **1984**, 49, 561. Treatment of the dione with 2,2-dimethyl-1,3-propanediol (1 equiv) in the presence of *p*-TsOH gave the expected mixture of compounds, which were separated readily by column chromatography. Recycling of the dione and the diketal made the overall process quite efficient.

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11 In this conversion, *tert*-butyldimethylsilyl triflate proved to be a far more efficient and less capricious silylating agent than the corresponding chloride.

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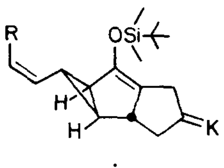
13 Our original synthetic plan called for the preparation and thermal rearrangement of **i** which, if successful, would be expected to produce **ii**. However, the presence of a *cis* alkyl group (even a methyl group) on the vinyl side chain proved to be very deleterious to the rearrangement process, since thermolysis of substances of general structure **i** failed to produce any products of general structure **ii**.



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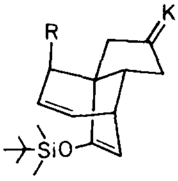

ii

14 The stereochemical assignments for **12** and **13** were based on spectral data and chemical transformations. Details will be given in a full paper.

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17 In terms of avoiding carbon-carbon double reduction, the use of methylamine was preferable to the use of ethylamine.

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19 Hydrogenation of **18** in ethanol or tetrahydrofuran provided very poor yields of the desired ketal aldehyde.

20 This material exhibited melting point and spectra identical with those of (±)-**19** synthesized by Burke *et al.*[3c] We are very grateful to Professor Burke for copies of the spectra of (±)-**19**.

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