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SYNTHESIS OF ROOPEROL [1,5-BIS(3′,4′-DIHYDROXYPHENYL)PENT-1-EN-4-YNE]

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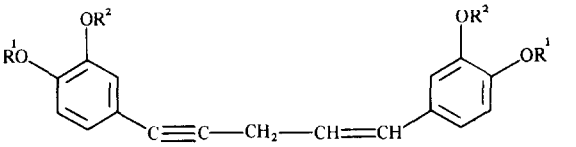
Key Word Index—*Hypoxis* spp., hypoxoside, rooperol; *tert*butyldimethylsilyl ether, pentenyne

Abstract—Rooperol, a phenolic compound bearing the pentenyne moiety, has been synthesized from simple starting materials via a nine step synthesis. A crucial step in the synthesis involves protection of the phenolic groups as the *tert*butyldimethylsilyl ether derivative.

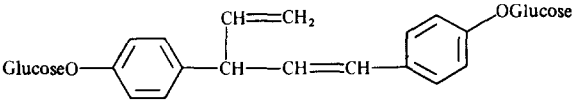
INTRODUCTION

Extractives from a variety of *Hypoxis* species have aroused considerable interest in the recent literature on account of their unusual structure and also because of the known use of *Hypoxis* extracts in African traditional medicine. Infusions of this plant are used, for example, against urinary infections and internal parasites [1]. From *Hypoxis obtusa*, Marini Bettolo and his coworkers [2] have isolated the novel diglucoside (**1**) and named it hypoxoside and more recently these researchers [3] have obtained a related compound (**2**), named nyasoside, from *Hypoxis nyasica*. Our own interest in this area stems from the reported activity of *Hypoxis* extractives against lymphocytic leukaemia [4] and from our observations that the extractives also possess antibacterial properties [5, 6]. These properties are not entirely unexpected when one takes into account the known antibiotic [7] hypnotic [8], antifertility [9] and anti-fungal [10] properties of compounds possessing functionalities related to those found in rooperol.

To reach a better understanding of the structure–activity factors involved, particularly with regards to cytotoxic/cytostatic activity, we have embarked on a comprehensive programme involving the synthesis of substituted pent-1-en-4-ynes and closely related analogues. By utilising standard alkyne coupling reactions we were able to synthesize 1,5-bis[3′,4′-dimethoxyphenyl)pent-1-en-4-yne] (**3**) as a first step in this direction [11]. Our attempts at demethylation, to afford the tetrahydroxy compound, rooperol (**4**), met with only limited success. The pent-1-en-4-yne system is sensitive to acid and base reagents [12] and standard demethylating reagents such as boron tribromide and other Lewis acids all resulted in destruction of this system. Some success was finally achieved by an adaptation of the procedure described by Minamikawa and Brossi [13] but conversion only took place to an extent of 20% [Drewes, S. E. and Scogings, U. J., unpublished results]. In this procedure tetramethoxy-rooperol (**3**), quinoline and trimethylsilyl iodide were heated in a nitrogen atmosphere for extended periods at 180°.



1 R^1 = Glucose, R^2 = H
3 R^1 = Me R^2 = Me
4 R^1 = H R^2 = H



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RESULTS AND DISCUSSION

In this paper we describe the successful synthesis of rooperol (**4**) through the use of *tert*butyldimethylsilyl ether as protecting group [14]. This group is about 10^4 more stable with regards to the Si-O bond than the trimethylsilyl group, yet is readily cleaved with *n*-tetraalkylammonium fluoride at low temperatures. Effective deprotection conditions have been described by Cooke [15].

An outline of the synthesis of rooperol (**4**) is given in the Scheme. Compared with the earlier published synthesis of tetramethoxy rooperol (**3**) the present approach incorporates distinct advances. These include: (i) a protecting group amenable to removal in the final step without undue disruption of the pentenyne moiety. (ii) Use of 1-bromo-3-[3′,4′-di(tertbutyldimethylsiloxy)-phenyl]prop-2-ene as an intermediate (Scheme) rather than the corresponding chloro derivative. Not only is the bromo derivative more reactive in Li-initiated C–C coupling but it also proved to be more amenable to

manipulation and could be obtained in high (60%) yield (iii) An improved procedure for synthesis of the 3,4-disubstituted phenyl acetylene derivative Our previous route [11] had involved a classical dehydrogenation of a vinyl bromide to an alkyne with potassium hydroxide as base [16] In this instance the shorter procedure developed by Corey [17], involving initial reaction of the aldehyde with activated zinc, triphenylphosphine and carbon tetrabromide was adopted This afforded the dibromostyrene in 80% yield and the latter was transformed with butyl lithium to the desired acetylene in 60% yield

An interesting feature relating to the final coupling of the two halves of the target molecule (Scheme) concerns the inability of the alkyne 'half' to generate the alkynide anion through the action of ethyl magnesium bromide or *n*-butyl lithium When *tert*butyl lithium was substituted the desired anion formed and C–C coupling subsequently occurred in overall 35% yield Deprotection still posed problems and despite numerous variations the treatment with tetraethylammonium fluoride gave a best transformation to rooperol (**4**) amounting to 35%

Toxicity tests carried out on naturally occurring hypoxoside using rats and mice as test animals indicated very high survival rates Cytotoxic studies on hypoxoside on HeLa cells showed inhibition at concentrations of 12 5 μg/ml and similar results were obtained for rooperol on P-31 cell lines at 10 μg/ml These results, done in collaboration with Dr H Kundig, Department of Pharmacology, University of Witwatersrand, will be published separately

EXPERIMENTAL

Mps are uncorrected ^{1}H NMR spectra were recorded using $CDCl_3$ as solvent and TMS as int standard, unless otherwise indicated

3-[3′,4′-*Di*(tert*butyldimethylsiloxy*)*phenyl*]-*ethyl*-2-*propenoate* (**5**) The ethyl ester, prepared from caffeic acid (3 5 g), was dissolved in DMF (8 ml) under N_2 A mixture of *tert*butyldimethylsilyl chloride (5 6 g) and imidazole (5 01 g) in dry DMF (10 ml) was added dropwise and the reaction left at ambient temp for 20 hr whereafter it was quenched with H_2O Extraction with ether, drying over $MgSO_4$ and concn *in vacuo* gave 7 1 g of an oil which was chromatographed over SiO_2 (hexane–EtOAc, 2 1) to yield 6 5 g (89%) of crystalline material mp 104–107° IR ν_{max}^{KBr} cm^{-1} 1700 (C=O), 1630 (C=C), 1125 (Si–O) ^{1}H NMR (80 MHz) δ0 22 (12H, SiMe), 0 99 (18H, s, Si + Me), 1 33 (3H, *t*, *J* = 7 1 Hg, $CH_2\underline{Me}$), 4 25 (2H, *q*, *J* = 7 1 Hz, $\underline{CH_2}$Me), 6 22 (1H, *d*, *J* = 15 9 Hz, CH=C$\underline{H}$CO), 6 86–7 03 (3H, *m*, ArH), 7 57 (1H, *d*, *J* = 15 9 Hz, C$\underline{H}$=CHCO) EIMS 70 eV, *m/z* (rel int) 436 [M]$^+$ (4 3), 73 (100) (Found 436 24540, $C_{23}H_{40}O_4Si_2$ requires 436 24650)

3-[3′,4′-*Di*(tert*butyldimethylsiloxy*)*phenyl*]*prop*-2-*en*-1-*ol* (**6**) To compound **5** (2 0 g) in toluene (6 ml) at −78° under N_2 was added a 2 2 molar excess of *diiso*butylaluminium hydride (1 4 g, 1 8 ml) in toluene (6 ml) over a period of 1 hr After 30 min at ambient temp the reaction was quenched with saturated NH_4Cl Ether extraction gave a light yellow oil which was purified by SiO_2 chromatography (see above) to give 1 3 g (72%) of oil IR ν_{max}^{neat} cm^{-1} 3325 (OH), 1600 (C=C), 1130 (Si-O) ^{1}H NMR (80 MHz) 0 20 (12H, s, Si-Me), 0 99 (18H, s, Si + Me), 1 64 (1H, *br s*, $CH_2\underline{OH}$), 4 27 (2H, *d*, J = 5 4 Hz, $\underline{CH_2}$OH), 6 30 (1H, d$\underline{t}$, *J* = 15 9 Hz, and *J* = 5 4 Hz, $CH_2C\underline{H}$=CH), 6 50 (1H, *d*, *J* = 15 9 Hz, CH_2–CH=C$\underline{H}$), 6 80–6 90 (3H, *m*, Ar$\underline{H}$) EIMS 70 eV, *m/z* (rel int) 394 [M$^+$] (11), 205 (100), (Found 394 23520 $C_{21}H_{38}O_3Si_2$ requires 394 23528)

1-*Bromo*-3-[3′,4′-*di*(tert*butyldimethylsiloxy*)*phenyl*]*prop*-2-*ene* (**7**) Triphenylphosphine (658 mg) in acetonitrile (3 ml) was cooled in an ice bath and bromine (406 mg) added dropwise over 15 min The ice bath was then removed and (**6**) (1 0 g) in dry acetonitrile (4 ml) added over 20 min After stirring at room temp for 30 min the reaction mixture was filtered through a short SiO_2 column The eluate was concd and purified by CC as before to yield a pale yellow oil (600 mg 52%) IR ν_{max}^{neat} cm^{-1} 1610 (C=C) ^{1}H NMR (80 MHz) 0 20 (12H, *s*, Si-Me) 0 99 (18H, s, Si + Me), 4 15 (2H, *d*, *J* = 7 0 Hz, CH_2Br), 6 20 (1H, *dt*, *J* = 7 0 Hz and *J* = 15 6 Hz, CH=C$\underline{H}$CH$_2$Br), 6 55 (1H *d*, *J* = 15 6 Hz, C$\underline{H}$=CHCH$_2$Br), 6 76-6 94 (3H, *m*, ArH) EIMS 70 eV, *m/z* (rel int) 457/459 [M]$^+$ (1), 41(100) (Found 457 15990 $C_{21}H_{38}BrO_2Si_2$ requires 457 15936)

3′,4′-*Di*(tertbutyldimethylsiloxy)phenylacetylene (**9**) As starting material for **9**, 3,4-dihydroxybenzaldehyde was used Following silylation by the procedure described for **5**, it was converted to the dibromostyrene derivative (**8**) by Corey's procedure [17] To a solution of (**8**) (3 0 g) in dry THF (10 ml) at −78 under N_2 *n*-butyl lithium (9 7 ml, 2 1 equiv) was added over 60 min After stirring 20 min at room temp, the reaction was quenched (NH_4Cl), extracted with EtOAc and the combined organic extracts concentrated *in vacuo* after drying ($MgSO_4$) Following CC a yellow oil (1 25 g, 60%) was isolated IR ν_{max}^{neat} cm^{-1} 2190 (C≡C), 1125 (Si-O), 835 (Si-C) ^{1}H NMR (80 MHz) 0 20 (12H, *s*, Si-Me), 0 99 (18H, s, Si + Me), 2 95 (1H, s, C≡CH), 6.69–7 05 (3H, *m*, ArH) (Found 362 20980, $C_{20}H_{34}O_2Si_2$ requires 362 20972)

1,5-*Bis*[3′,4′-*di*(tert*butyldimethylsiloxy*)*phenyl*]*pent*-1-*en*-4-*yne* (**11**) To a solution of **9** (230 mg) in dry THF (2 ml) at −78 under N_2 was added *tert*butyl lithium (0 7 ml, 2 2 equiv) over 20 min Anhydrous Cu(I) Cl (5 mg) was added and the reaction mixture stirred for 10 min at room temp Compound (**7**) (144 mg) in dry THF (3 ml) was added dropwise to the mixture and it was then refluxed for 15 min before quenching with aqueous NH_4Cl (1 g) and KCN (0 1 g) Extraction with ether, drying and concentration at reduced pressure gave an orange oil which required purification by CC (hexane–ethyl acetate, 6 1) This gave a light orange oil (115 mg, 35%) IR ν_{max}^{neat} cm^{-1} 2190 (C≡C), 1590 (C=C), 1120 (Si-O), 840 (Si-C) ^{1}H NMR (80 MHz) 0 20 (24H, *s*, SiMe), 0 99 (36H, s, Si + Me), 3 27 (2H, *dd*, *J* = 5 4 Hz and *J* = 1 6 Hz, –CH_2–), 6 02 (1H, *dt*, *J* = 15 6 Hz and *J* = 5 6 Hz, CH=C$\underline{H}$CH$_2$), 6 47–6 64 (1H, *m*, CH=C$\underline{H}$Ph), 6 80–6 97 (6H, *m*, Ar$\underline{H}$)

1,5-*Bis*(3′,4′-*dihydroxyphenyl*)*pent*-1-*en*-4-*yne* (**4**) The silyl ether (**11**) (100 mg) in dry THF (2 ml) was treated dropwise at room temp with an excess of tetraethylammonium fluoride After 45 min TLC indicated that reaction was complete and the mixture was then washed through a short SiO_2 column with THF Further purification on SiO_2 was necessary (hexane–ethyl acetate, 4 1) and this gave 35 mg of a light brown oil IR ν_{max}^{neat} cm^{-1} 3400 (OH), 2195 (C≡C), 1610 (C=C) ^{1}H NMR (80 MHz) 3 26 (2H, *dd*, *J* = 5 4 Hz and J = 1 6 Hz, CH_2), 6 07 (1H, *dt*, *J* = 15 9 Hz and *J* = 5 4 Hz, H_α), 6 58 (1H, *d*, *J* = 15 9 Hz, H_β), 6 75–6 94 (6H, *m*, ArH) (Found 282 08896, $C_{17}H_{14}O_4$ requires 282 08921) The above compound was indistinguishable from an authentic sample obtained from the hydrolysis of hypoxoside with β-glucosidase

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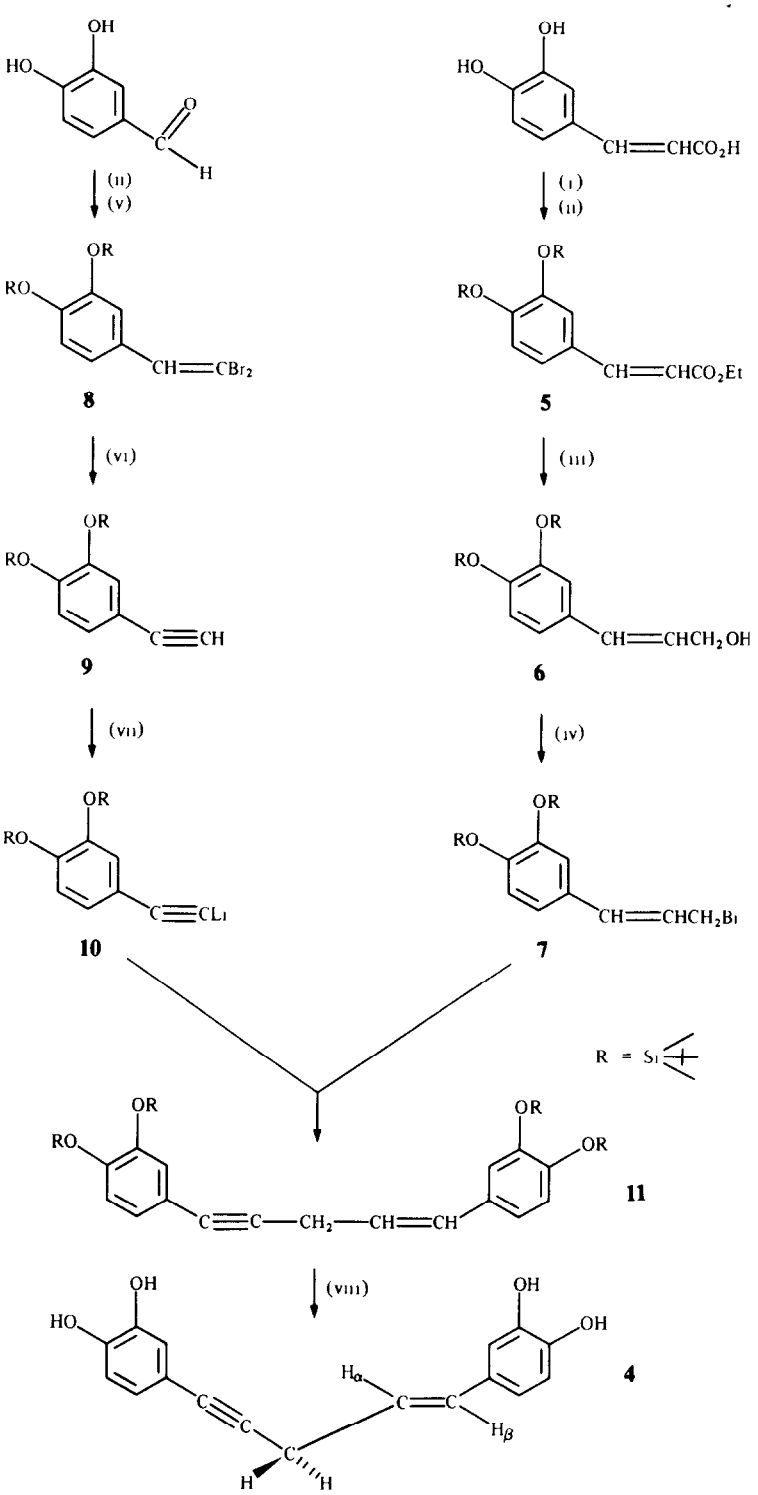

Reagents (i) EtOH / H^+, (ii) Imidazole, ClSi, (iii) DIBAH, (iv) Ph_3P, Br_2, (v) Zn, Ph_3P, CBr_4, (vi) *n*BuLi, (vii) *t*BuLi, (viii) $Et_4N^+ F^-$

REFERENCES

1 Watt, J M and Breyer-Brandwijk, M (1969) in *The Medicinal and Poisonous Plants of Southern and East Africa*, p 41 E and S Livingstone, London
2 Marini Bettolo, G B, Patamia, M, Nicoletti, M, Galeffi, C and Messana, I (1982) *Tetrahedron* **38**, 1683
3 Marini Bettolo, G B, Nicoletti, M, Messana, I, Galeffi, C, Msonthi, J D and Chapya, W A (1985) *Tetrahedron* **41**, 665
4 Barclay, A and Perdue, R E (1976) *Cancer Treatment Rep* **60**, 1081
5 Drewes, S E and Liebenberg, R W (April 1983) Brit Pat., No 8211293
6. Drewes, S E and Liebenberg, R W (April 1983) Brit Pat, No 83103765
7 Prevost, S, Meier, J, Chodkiewicz, W, Cadiot, P and Willemart, A (1961) *Bull Soc Chim France* 2171
8 Klosa, J (1957) *Angew Chem* **69**, 135
9 Fusetani, N., Kato, Y, Matsunaga, S and Hashimoto, K (1983) *Tetrahedron Letters* **24**, 2771
10 Reisch, W, Spitzner, W and Schulte, K E (1967) *Arzneim-Forsch* **17**, 816
11 Drewes, S E, Hall, A J, Learmonth, R A and Upfold, U J (1984) *Phytochemistry* **23**, 1313
12 Klein, J and Brenner, S (1969) *J Am Chem Soc* **91**, 3094
13 Minamikawa, J and Brossi, A (1978) *Tetrahedron Letters* 3085
14 Corey, E J and Venkateswarlu, A (1972) *J Am Chem Soc* **94**, 6190
15 Kendall, P M, Johnson, J V and Cook, C E (1979) *J Org Chem* **44**, 1421
16 Hessler, J C (1941) in *Organic Synthesis, Collective Volume I* (Blatt, A H, ed), p 438 John Wiley, New York
17 Corey, E J and Fuchs, P L (1972) *Tetrahedron Letters* 3769