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TOTAL SYNTHESIS OF DIOSPYROL
AN ANTHELMINTIC DRUG FROM *DIOSPYROS MOLLIS* GRIFF

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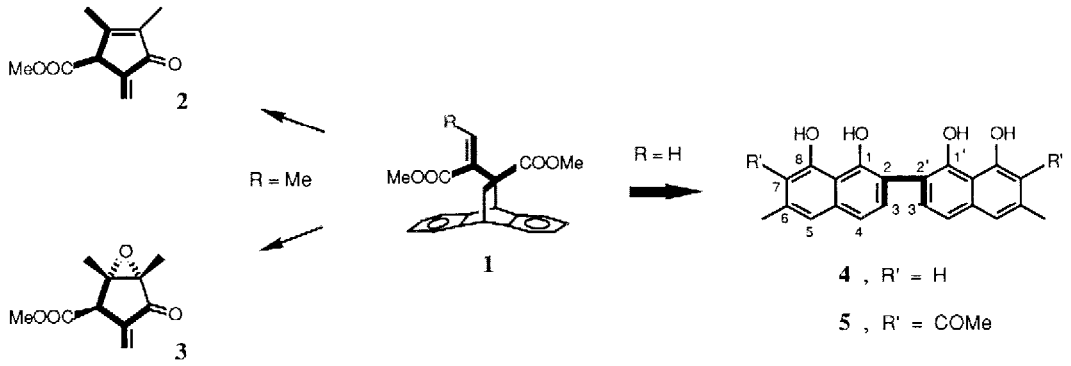
Abstract : Diospyrol **4** is constructed from a masked butadiene synthon, anthracene adduct **1** [R = H]. The key construction steps comprise tandem Michael addition-Dieckmann condensations, first between anion **7** and **1**, and subsequently between anion **7** and **15**.

In the previous communication [1] we described a straightforward synthesis of deepoxy-4,5-didehydromethyleno mycin A and methylenomycin A methyl esters, **2** and **3** respectively, from anthracene adduct **1** [R = Me]. To further elaborate the usefulness of anthracene adducts we report here a short and convenient total synthesis of **Diospyrol 4**, starting from **1** [R = H].

Scheme I

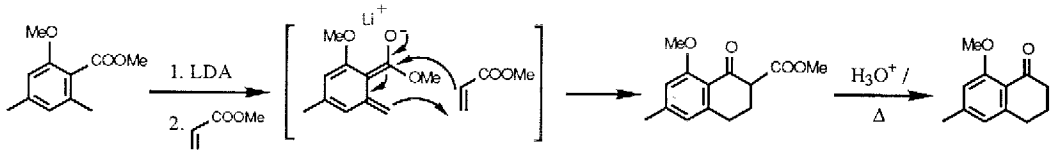


Diospyrol, a dimeric naphthol derivative with alleged anthelmintic property, is obtained from the berry of *Diospyros mollis*, [2] an indigenous plant widely distributed throughout Southeast Asia. The Diospyros berry has been extensively used in Thailand for treating hook-worms since ancient times, until suddenly, over a decade ago, cases of blindness were reported in a mass chemotherapy programme conducted by the Ministry of Health, which threw confusion and uncertainty

over the continued use of the berry. Coincidentally a toxic compound, **stypandrol** or " blindgrass toxin " **5** [isolated from an Australian plant *Stypandra imbricata* or " blindgrass "] [3] which has a similar structure to diospyrol **4**, is reported to cause blindness in animals when ingested. Naturally it became of interest to synthesize diospyrol **4**, stypandrol **5**, and their derivatives for a study of structure-reactivity relationships.

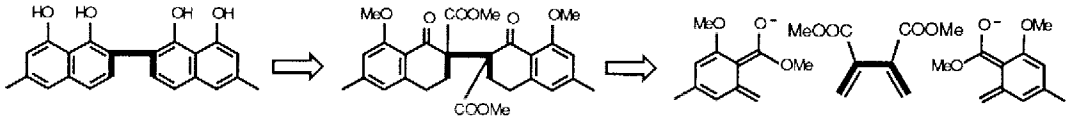
A former synthesis of diospyrol, reported by Govindachari, [4] utilized classical manipulations which gave a poor overall yield. An improved method, recently developed by the Australian group, [5] delivers stypandrol **5** via Fries rearrangement of 1,1'-dimethoxy-8,8'-diacetyldiospyrol followed by demethylation. Our synthesis evolved from our prior observation that 8-methoxy-1-tetralones, e.g. **9**, can easily be obtained in a one-pot process from the reaction between toluate anion **7** [6] and acrylic ester as shown in **Scheme II**. [7] Using a retro-synthetic approach, we dissected symmetrical diospyrol **4** into a central four carbon synthon [drawn in heavy line in **Scheme III**] and identical left and right ring synthons. Since anthracene adduct **1** yields 2,3-dicarbomethoxybutadiene **11** upon flash vacuum pyrolysis, [8] it nicely provides the requisite four central carbon unit upon which to construct the left and right naphthol rings by the annulation reaction of the type shown in **Scheme II**.

Scheme II



6 **7** **8** **9**

Scheme III

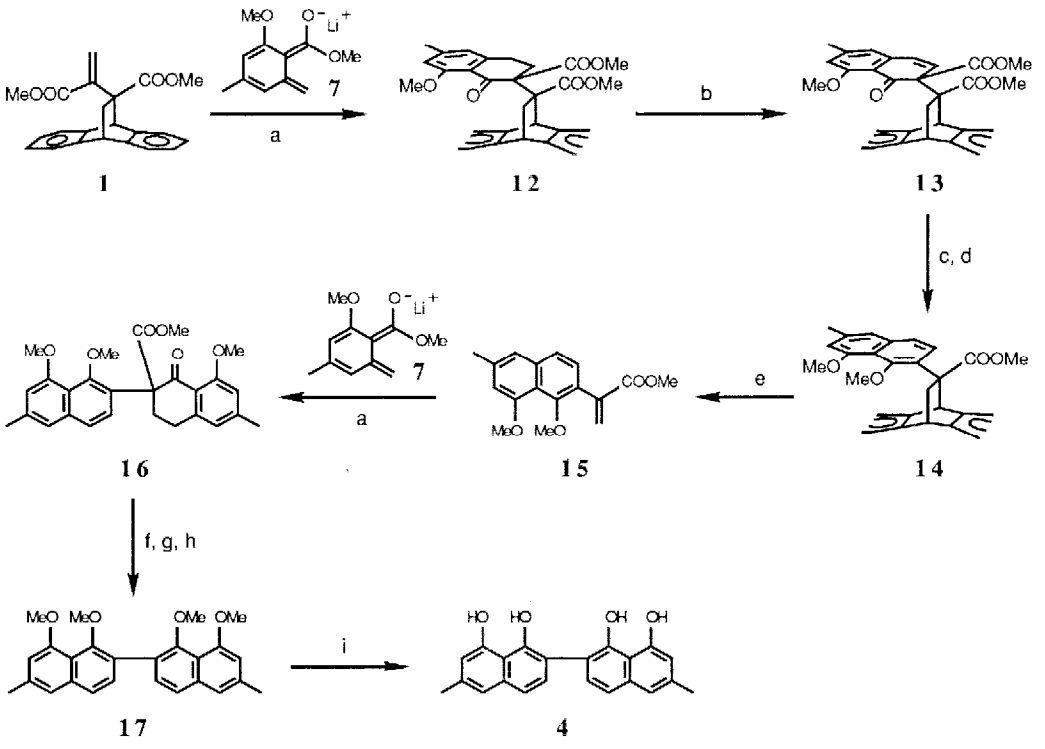


4 **10** **7** **11** **7**

Addition of diene **11** [1 eq.] to anion **7** [2 eq.] in THF solution at -78° with prolonged stirring at various temperatures consistently gives complex mixtures. However, treating the diene precursor **1** [R = H] with an equimolar amount of **7** at -78° and leaving the reaction mixture to stir overnight at room temperature cleanly yields **12** as a mixture of two separable isomers [**12a** and **12b**, ratio 1:2 ; silica gel, 25% ethyl acetate in hexane as eluant; 80%]. Both isomers fail to undergo the hydrolysis-decarboxylation reaction under the acidic conditions earlier employed, [7] but can be dehydrogenated with DDQ in boiling dioxane to give **13a** (60% from **12a**) and **13b** (50% from **12b**) respectively. Compounds**13a** and **13b** can then be hydrolysed, decarboxylated and converted into the 1,8-dimethoxynaphthalene derivative **14** [colourless solid mp. 187-189° from a dichloromethane-hexane mixture; 48 and 52% from **13a** and **13b**

respectively]. Flash vacuum pyrolysis of **14** gives analytically pure vinylnaphthalene **15** in 92% yield. Its nmr spectrum clearly indicates the presence of an aromatic methyl at δ 2.44, three methoxy groups [δ 3.72, 3.78, and 3.94], two vinylic protons at δ 5.77 and 6.32 [J = 2 Hz], and four aromatic protons as two doublets [δ 6.68 and 7.16; J = 1.5 Hz] and an AB quartet at δ 7.22 and 7.47 [J = 9 Hz].

Scheme IV



a) THF / -78° → r.t. overnight ; b) DDQ / dioxane / reflux ; c) 30% aq. NaOH / EtOH / THF / RT ; d) Me_2SO_4 / K_2CO_3 / acetone / reflux ; e) 500° / 0.01 mm ; f) 30% NaOH / dioxane-MeOH / Δ then H_3O^+ ; g) $(MeO)_3CH$ / TsOH / MeOH / Δ ; h) DDQ / benzene / r.t. ; i) BCl_3 / CH_2Cl_2 / -60° → RT

With **15** in hand, the simple task remaining is to repeat the annulation sequence once more. Thus treatment of **15** with **7** as previously described gives rise to **16** [74%] which, after hydrolysis and decarboxylation, is converted into the corresponding enol ether [9] and finally dehydrogenated with DDQ to yield diospyrol tetramethylether **17** [67%] [10] which possesses physical properties identical in all respects with an authentic sample. Boron trichloride demethylation [4] of **17** completes the synthesis of the target diospyrol **4** in 85% yield. However, because diospyrol is rather unstable and can be easily air-oxidised, it is preferable to store the compound in the form of its tetramethylether **17** , especially for

transportation purposes. Diospyrol can then be freshly generated just before use. Various derivatives of **4** are currently being synthesized for biological testing.

The use of adduct **1** in the above synthesis represents an unconventional mode of construction of the aromatic naphthol nucleus, i.e. via a tandem Michael addition-Dieckmann condensation process instead of the customary electrophilic substitution. The synthesis of diospyrol outlined above thus serves to emphasize the versatility of anthracene adducts in organic synthesis.

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References :

A preliminary account of this work was presented at the 22nd Sheffield Stereochemistry Symposium , 14 December 1988.

1. Preceeding Communication.
2. Activity : a) S. Daengsvang, M. Mangalasmaya, *Ann. Trop. Med. & Parasit.*, 1941, **35**, 43 ; b) E. H. Sadun, S. Vajrasthira, *J. Parasit.*, 1954, **40**, 49.
   Structure : a) J. W. Loder, S. Mongkolsuk, A. Robertson, W. B. Whalley, *J. Chem. Soc.*, 1957, 2233 ;
   b) K. Yoshihira, S. Natori, P. Kanchanapee, *Tetrahedron Lett.*, 1967, 4857. ; c) L. Borsub, S. Ruchirawat, C. Sadavongvivad, Y. Thebtaranonth, *Tetrahedron Lett.*, 1976, 105.
3. S. M. Colegate, P. R. Dorling, C. R. Huxtable, *Phytochemistry*, 1986, **25**, 1245.
4. T. R. Govindachari, N. Viswanathan, K. R. Ravindranath, B. Anjaneyulu, *Indian J. Chem.*, 1973, **11**, 1081.
5. M. A. Rizzacasa, M. V. Sargent, *Aust. J. Chem.*, 1988, **41**, 1087.
6. a) F. M. Hauser, R. P. Rhee, S. Prasanna, *Synthesis*, 1980, 72 ; b) T. A. Carpenter, G. E. Evans, F. J. Leeper, J. Staunton, M. R. Wilkinson, *J. Chem. Soc. , Perkin Trans. 1*, 1984, 1043.
7. B. Tarnchompoo, C. Thebtaranonth, Y. Thebtaranonth, *Synthesis*, 1986, 785.
8. B. Tarnchompoo, C. Thebtaranonth, Y. Thebtaranonth, *Tetrahedron Lett.*, 1987, **28**, 6671.
9. S. K. Pradhan, H. J. Ringold, *J. Org. Chem.*, 1964, **29**, 601.
10. Application of the f, g, h reaction sequence [see conversion of **16** → **17**] to **12** gave a much lower yield of **14** than that obtained by the described b, c, d route.

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