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Facile Transformation of 1-Methoxynaphthalenes to Octahydrophenanthrenes Application to the Total Synthesis of (±)-Sempervirol Methyl Ether, (±)-Sugiol Methyl Ether, (±)-Nimbiol Methyl Ether, and (±)-Nimbidiol Dimethyl Ether

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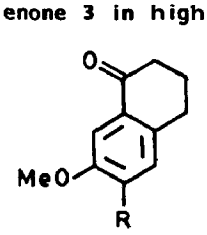
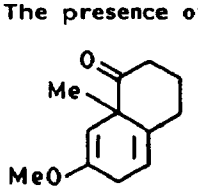
Abstract : An efficient general method has been developed for the synthesis of the tricyclic aromatic ketones **4**,12,13 and **14** from the 1-methoxynaphthalenes 8,9,10 and 11 respectively. The transformations of the ketones **4**,12,13 and **14** into the diterpene ethers (±)-sempervirol methyl ether (7), (±)-sugiol methyl ether (15), (±)-nimbiol methyl ether (16), and (±)-nimbidiol dimethyl ether (17) have been successfully accomplished involving reductive methylation in liquid ammonia as the key reaction.

Several aromatic ketones, e.g. 1-tetralones[1,2], 1-indanones[3,4] etc. undergo facile reductive alkylation in anhydrous ammonia under appropriate experimental conditions to generate angularly alkyl substituted dienones in high yields. During such reductive alkylation of aromatic ketones in liquid ammonia, a methoxy group which is at the para position with respect to the carbonyl group is invariably lost due to hydrogenolysis[5]. Reductive methylation of the tetralones 1 and 2, for example, provides the same dienone 3 in high yields. The presence of a p-OMe group, however,



1, R=H
2, R=OMe



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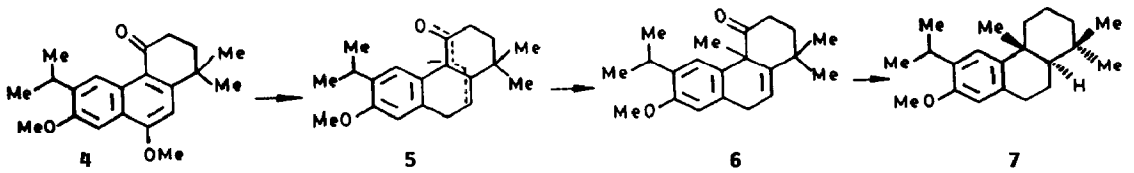
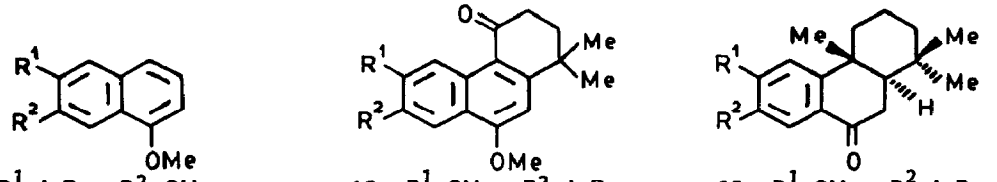
often renders the preparation of a desired aromatic ketone more convenient. We reasoned that starting from 1-methoxynaphthalenes, the preparation of 1,1-dimethyl-9-methoxy-1,2,3,4-tetrahydrophenanthren-4-ones would be facile due to the presence of the 1-OMe group and reductive methylation of such tetrahydrophenanthrenones, appropriately substituted in ring A, would provide potential intermediates for the total synthesis of a number of tricyclic diterpenes possessing octahydrophenanthrene skeleta. It was envisaged that the tetrahydrophenanthrenone **4** would undergo hydrogenolysis of the 9-OMe group in metal-ammonia solution to generate the enolate anion 5 which on methylation would afford the β,γ-unsaturated ketone **6**. The removal of the carbonyl group from **6** followed by hydrogenation of the double bond in ring B was



4 5 6 7

then expected to lead to a total synthesis of the tricyclic diterpene ether (±)-sempervirol methyl ether (7)[6]. We now report efficient synthesis of the 9-methoxy-tetrahydrophenanthrenones 4,12,13 and 14 from the 1-methoxynaphthalenes 8,9,10 and



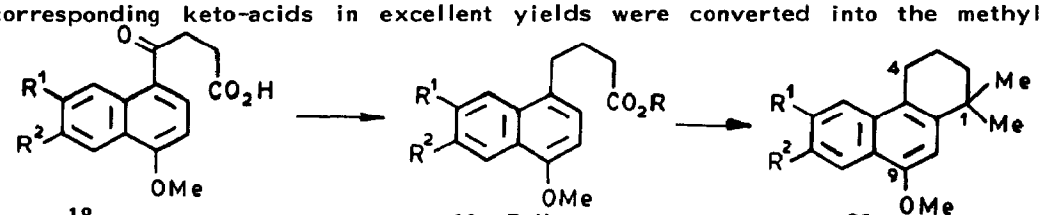
8, R^1=i-Pr, R^2=OMe
9, R^1=OMe, R^2=i-Pr
10, R^1=OMe, R^2=Me
11, R^1=R^2=OMe

12, R^1=OMe, R^2=i-Pr
13, R^1=OMe, R^2=Me
14, R^1=R^2=OMe

15, R^1=OMe, R^2=i-Pr
16, R^1=OMe, R^2=Me
17, R^1=R^2=OMe

11 and successful conversion of the aromatic ketones 4,12,13 and 14 into the tricyclic diterpene ethers (±)-sempervirol methyl ether (7)[7], (±)-sugiol methyl ether (15)[8], (±)-nimbiol methyl ether (16)[9], and (±)-nimbidiol dimethyl ether (17)[10] respectively using reductive methylation in liquid ammonia as the key reaction.

Succinoylation of 8 in the presence of anhydrous $AlCl_3$ furnished the keto-acid 18a[11], m.p. 177-178°C in 76% yield. The keto-acids 18b (m.p. 183-184°C), 18c (m.p. 191-192°C), and 18d (m.p. 196°C) were prepared in a similar manner from the 1-methoxynaphthalenes 9, 10 and 11 respectively in high yields. Reduction of 18a with $NaBH_4$ in aqueous alkali followed by catalytic hydrogenolysis (H_2, 10% Pd-C) of the crude product in AcOH furnished the acid 19a (88%), m.p. 166-167°C which was converted into the methyl ester 20a, m.p. 57-58°C. The acids 19b (m.p. 129-130°C), 19c (m.p. 165-166°C), and 19d (m.p. 169-170°C), similarly prepared from the corresponding keto-acids in excellent yields were converted into the methyl esters



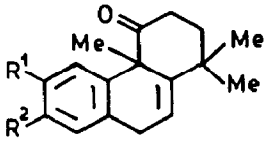
18 19, R=H → 20, R=Me 21

18a,19a,20a,21a : R^1=i-Pr, R^2=OMe
18b,19b,20b,21b : R^1=OMe, R^2=i-Pr
18c,19c,20c,21c : R^1=OMe, R^2=Me
18d,19d,20d,21d : R^1=R^2=OMe

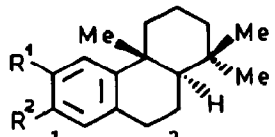
20b (m.p. 56-57°C), **20c** (m.p. 106-107°C), and **20d** (m.p. 91-92°C) respectively. Treatment of **20a** with MeMgI (4 equiv.) in refluxing Et_2O followed by cyclisation of the resulting carbinol with polyphosphoric acid furnished the tetrahydrophenanthrene derivative **21a**, m.p. 69-70°C in 82% yield. The transformations of the esters **20b**, **20c** and **20d** into the tetrahydrophenanthrenes **21b** (m.p. 153-154°C), **21c** (m.p. 133-134°C), and **21d** (m.p. 189-190°C) respectively were similarly carried out in high yields. Oxidation at C-4 of the tetrahydrophenanthrenes **21a-d** with pyridinium chlorochromate in CH_2Cl_2 was extremely facile due to the presence of the p-OMe group at C-9 and provided the aromatic ketones **4** (m.p. 140-141°C), **12** (m.p. 163-164°C), **13** (164-165°C), and **14** (m.p. 209-210°C) respectively in very high yields (87-90%).

Reductive methylation[12] of the tetrahydrophenanthrenone **4** in liquid ammonia afforded the β,γ-unsaturated ketone **6**, m.p. 121-122°C in 95% yield. Huang-Minlon reduction of **6** followed by catalytic hydrogenation of the product in AcOH and subsequent chromatography over silica gel[7] furnished (±)-sempervirol methyl ether (**7**) in 55% yield, m.p. 62-63°C; the cis-fused octahydrophenanthrene **28** was also isolated in 30% yield.

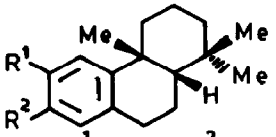
Reductive methylation of the aromatic ketones **12**,**13** and **14** provided **22**,**23** and **24** respectively in excellent yields. Huang-Minlon reduction of **22** followed by catalytic hydrogenation and chromatography over silica gel afforded (±)-ferruginol methyl ether (**25**) in 55% yield; the cis-fused octahydrophenanthrene derivative **29**, m.p. 68-69°C was also isolated in 32% yield. Oxidation of **25** with CrO_3 in AcOH furnished (±)-sugiol methyl ether (**15**) (65%), m.p. 126-127°C. It may be mentioned in this connection that a synthesis of ferruginyl methyl ether constitutes[13,14] formal synthesis of a number of diterpenoid quinones.



22, R^1=OMe, R^2=i-Pr
23, R^1=OMe, R^2=Me
24, R^1=R^2=OMe



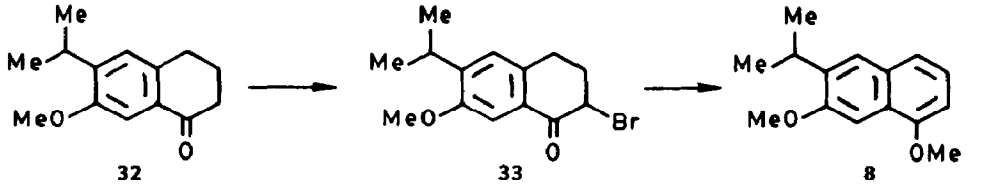
25, R^1=OMe, R^2=i-Pr
26, R^1=OMe, R^2=Me
27, R^1=R^2=OMe



28, R^1=i-Pr, R^2=OMe
29, R^1=OMe, R^2=i-Pr
30, R^1=OMe, R^2=Me
31, R^1=R^2=OMe

Huang-Minlon reduction of **23** followed by catalytic hydrogenation and chromatography over silica gel furnished **30** and **26** in 30% and 56% yields respectively. Similarly, **31** (30%) and **27** (55%), m.p. 87-88°C were obtained from **24** through Huang-Minlon reduction followed by catalytic hydrogenation. Oxidation of **26** and **27** with CrO_3 in AcOH afforded (±)-nimbiol methyl ether (**16**), m.p. 118-119°C and (±)-nimbidiol dimethyl ether (**17**), m.p. 110-111°C in 57% and 71% yields respectively. The identity of the octahydrophenanthrenes and octahydrophenanthrenones, mentioned above, were confirmed through comparison of ^1H NMR spectra with those of authentic samples.

The 1-methoxynaphthalene derivative **8** was conveniently prepared from 6-isopropyl-7-methoxy-1-tetralone (**32**)[15]. Bromination of the tetralone in ether[16] provided the corresponding 2-bromotetralone **33** (94%), m.p. 98-99°C which on dehydrobromination (LiBr, Li_2CO_3, dimethylformamide) followed by methylation (MeI, K_2CO_3,



32 **33** **8**

acetone) furnished **8** (84%). Similar methods were used to prepare the 1-methoxynaphthalenes **9** (m.p. 61-62°C), **10** (m.p. 79-80°C), and **11** (m.p. 137-138°C).

In conclusion, we have described a convenient general method for the synthesis of octahydrophenanthrene ring systems related to naturally occurring tricyclic diterpenes from easily accessible 1-methoxynaphthalenes. The utility of the present method has been amply demonstrated by total synthesis of several ring C-aromatic tricyclic diterpene ethers, e.g. (±)-sempervirol methyl ether, (±)-ferruginol methyl ether, (±)-sugiol methyl ether, (±)-nimbiol methyl ether, and (±)-nimbidiol dimethyl ether. Application of the present approach is currently being persued for the synthesis of the related tricyclic diterpenes taxodione and royleanone which possess antitumor cytotoxicity.

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