Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: R. H. Burnell , N. Dumont , N. Théberge & S. Desfossés (1992) Diterpenes of Azadirachta Indica. Syntheses to Confirm Structure, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:17, 2571-2578, DOI: 10.1080/00397919208021653

To link to this article: http://dx.doi.org/10.1080/00397919208021653

SYNTHETIC COMMUNICATIONS, 22(17), 2571-2578 (1992)

DITERPENES OF *AZADIRACHTA INDICA*. SYNTHESES TO CONFIRM STRUCTURE

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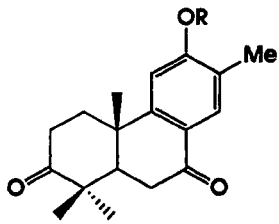
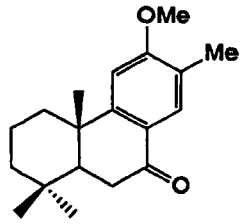
Abstract: The structure of the diterpene nimbinone **1b** has been confirmed by syntheses via a cascade cyclisation and also from podocarpic acid by two separate series of transformations. Synthesis of structure **3b** from dehydroabietic acid shows that this does not exhibit the properties described for nimbosodione.

Recent phytochemical studies have revealed a surprising number of new but simple diterpenes isolated from the various parts of *Azadirachta indica* [1]. The structures of these natural products are of course proposed following rigorous spectroscopic analysis but, as yet, only a few have been confirmed by synthesis. While investigating an approach to the more substituted candelabrone[2], we successfully exploited a preparative method involving cationic cyclisations of the type described by Livinghouse[3] and recently we have modified this procedure to afford products with no substituant at C.3. We felt that this expertise could lead rapidly to some of the new structures. To illustrate this, from the numerous examples in the literature we chose the synthesis of the 3,7-diketone, the bis-nor **1b**

(nimbinone)[4] since this structure appeared well substantiated and accessible by this synthetic route and could be corroborated by a parrallel preparation from a natural product. Furthermore, the same diene intermediate **6** would lead to another *A. indica* terpene, methyl nimbiol **2**[1] if cyclised under our modified conditions. The structure forwarded for the 16-nor compound **3b** (nimbosodione)[5] did not seem to match the spectroscopic data and its synthesis from natural (+)-dehydroabietic acid will show that our suspicions were well founded.



1a R = Me
1b R = H



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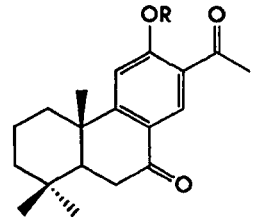
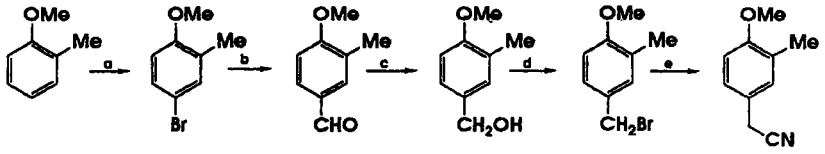


3a R = Me
3b R = H

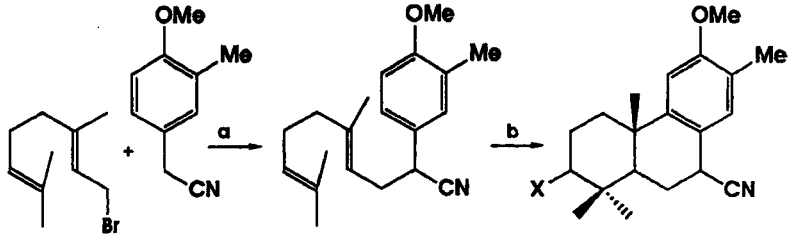
The skeletal unit for **1a** and **2** was readily prepared from the appropriate phenylacetonitrile **5** which was available from the corresponding o-methyl anisole as shown in Scheme I (reagents and conditions are given in reference[6]). The nitrile was then alkylated with geranyl bromide **4** and subsequently the diene sidechain of **6** was cyclised under cationic conditions to the tricyclic **7a.**

The transformation of **7a** to **1a** necessitates using the C.3 and C.7 functions for the introduction of the keto groups so first **7a** was converted to the anion (LDA prepared *in situ*) and oxygen was bubbled into the solution. The intermediate hydroperoxy cyano-

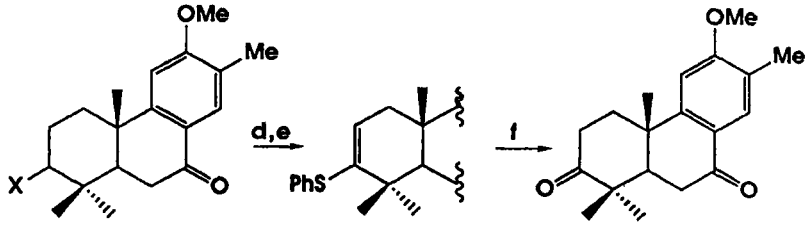


Scheme 1

hydrin was reduced affording the C.7 ketone **8a**. The phenylthio resdiue was then oxidised to the sulfoxide **8b** which upon treatment under the conditions of the Pummerer rearrangement led to the enol thio ether **9**. The latter was hydrolysed in the presence of $TiCl_4$ to give the (±)-3,7-diketone **1a** (Scheme 2 reagents see reference[7]) which was rigorously identical with the natural O-methyl nimbinone described by the Siddiqui group[4].



The diene **6** was also cyclised in BF_3/CH_3NO_2 but in the absence of methyl benzenesulfenate (Ph-S-OMe) and in this case the product was the tricyclic **7b** (87%). When the latter was oxidised as described previously for **7a** the ketone isolated was identical with methyl nimbiol **2**[8].



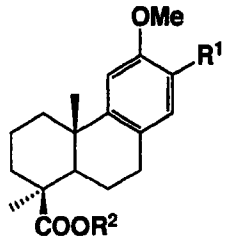
8a X = Ph-S **9** **1a**
8b X = Ph-S(O)

Scheme 2

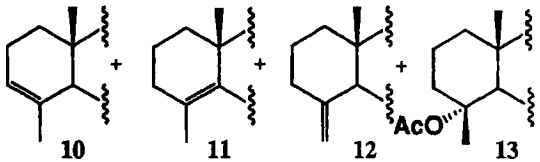
The structure of nimbinone was confirmed by another synthesis and in part our interest was to compare the two approaches. Since this second sequence started with natural podocarpic acid the final product is likely to have the proper absolute stereochemistry of the naturally occuring terpene. When methyl O-methylpodocarpate **9a** was subjected to the Duff reaction (for the reagents and conditions for this scheme see reference[9]) an almost quantitative yield of the aldehyde **9b** was obtained. The formyl residue was efficiently reduced to a methyl group affording **9c** and the ester in the latter was hydrolysed to the corresponding acid **9d.**

Lead tetracetate decarboxylation of the acid **9d** gave three inseparable olefins **10, 11** and **12** and the tertiary acetate **13.** Pyrolysis of the latter gave more of the same isomeric mixture of olefins which like Cambie[10] we separated by epoxidation which gave the three epoxides **14, 15** and **16** and the very useful and key intermediate, allylic alcohol **17.** More of the latter was prepared by the base catalysed isomerisation of the 3,4-epoxide **16** and by the

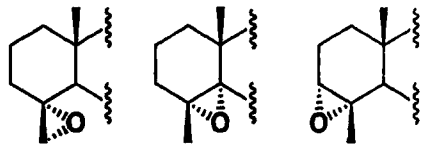
allylic oxidation of the 5,19-olefin **12** (some of which survived the per-acid oxidation). In this way the overall yield of **17** was about 20% from the acid **9d**.



9a R^1 = H R^2 = Me
9b R^1 = CHO R^2 = Me
9c R^1 = Me R^2 = Me
9d R^1 = Me R^2 = H



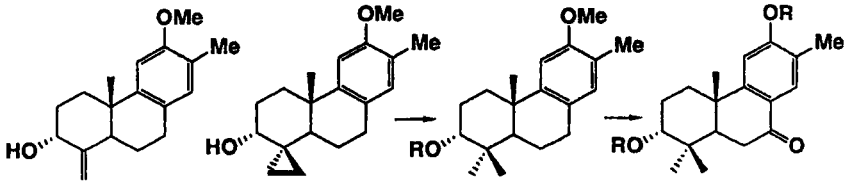
10 **11** **12** **13**



14 **15** **16**

The exocyclic double bond in **17** reacted readily with the Simmons-Smith reagent to afford the spiro-cyclopropyl derivative **18**. Conditions proven effective for the hydrogenolytic opening of the three-membered rings in similar substances[11] proved less disciminate than anticipated so apart from the desired gem-dimethyl compound **19a** the reaction mixture gave similar quantities of the compounds in which the aromatic ring had also been reduced. It was found advantageous to stop the hydrogenation early and in this way, allowing for the starting material recuperated, the yield of **19a** was a modest 40%. After protecting the hydroxyl group as the acetate **19b** the C.7 benzylic position was oxidised to give the ketone **20a** which by hydrolysis (**20b**) and oxidation with the Jones reagent afforded O-methyl-nimbinone **1a** identical in all respects with the

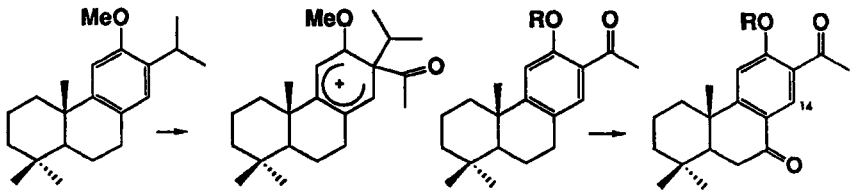
racemic sample from the previous synthesis except for its optical properties ($[\alpha]_D$ 19.7, c 1.0 $CHCl_3$).



17 18 19a R = H 20a R = Ac
19b R = Ac 20b R = H

The third structure **3b** was approached in a different fashion from the naturally occurring **21** which in reality we prepared from dehydroabietic acid by known procedures. Recently we have shown[12] that a 13-acetyl sidechain is readily introduced into such molecules by *ipso* acylation under Friedel-Crafts conditions to an intermediate formally equivalent to **22** which reverts to the aromatic species **23a** by preferential expulsion of the *iso*-propyl residue.

Since the experimental conditions (given in reference[13]) are also those for *peri* demethylation of aromatic ketones, the



21 22 23a R = Me 3a R = Me
23b R = H
23c R = Ac

Scheme 3

corresponding phenol **23b** and its acetate **23c** are also isolated from the reaction. Both are readily re-integrated into the synthesis by hydrolysis and/or methylation. Benzylic oxidation of **23a** (PCC in CH_2Cl_2) gave the C.7 ketone **3a**.

As suspected, it was immediately clear from the nmr spectra that the structure proposed[5] for the natural product could not be correct. The C.14 proton in the synthetic **3a** appeared as a singlet at 8.37 δ compared to the very low 7.81 δ given for the natural compound. More striking, the ^{13}Cmr resonances given for the aromatic ring carbons (δ 157.08, 159.08, 109.62, 159.15, 157.42 and 130.78 for C.8 to C.14) are inexplicably high when compared to the values found for the synthetic sample (126.89, 161.97, 106.00, 162.48, 124.32 and 130.00 δ resp.). No obvious structure springs to mind for the natural substance.

Acknowledgments: We thank the Québec Ministère de l'éducation (F.C.A.R.) for operating grants and we are grateful for graduate bursaries from the Natural Sciences and Engineering Research Council, Canada (to N.T.) and the Fondation Georges-Elie Amyot, Université Laval (to S.D.).

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6 Reagents for Scheme 1: (a) 18-crown-6, KBr, m-CPBA, CH_2Cl_2, 0°, 1h (b) THF, Mg then DMF reflux 5 min (c) $NaBH_4$, MeOH, r.t., 15 min (d) PBr_3, pyr, r.t., 3h (e) 18-crown-6, KCN, MeCN, 60°, 9h.

7 Reagents for Scheme 2: (a) LDA, THF, -78°, 3h (b) PhSOMe, $BF_3/MeNO_3$, -30° then 15°, 3.5h (c) LDA, THF, O_2, 1h then $SnCl_2/HCl$ 30 min (d) CH_2Cl_2, -78°, m-CPBA, 1h (e) CH_2Cl_2, 0°, $(CF_3CO)_2O$ then r.t., 9h (f) HOAc, $TiCl_4$ then reflux 1h.

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9 **9a** to **9b** : hexamethylenetetramine, CF_3COOH, 99%; **9b** to **9c** : Et_3SH, BF_3, CH_2Cl_2, 0°C, 15 min , 91%; **9c** to **9d** : LiI, 2,4,6-collidine, reflux, 5h, 100%; **9d** treated with $Pb(OAc)_4$, benzene, pyridine, reflux, 4 h gave acetate **13** (34%) and the mixture of **10, 11** and **12** (42%). Pyrolysis of **13** (240-260°) gave the mixed olefins (86%); Olefin mixt. **10, 11** and **12** plus m-CPBA in CH_2Cl_2 afforded **12** (15%), **14** (15%), **15** (36%), **16** (11%) and **17** (10%). **12** to **17** : SeO_2, 95% EtOH, reflux, 2 h, 88%; **16** to **17** : LDA, ether, reflux, 4 h, 87%; **17** to **18** : CH_2I_2, Et_2Zn, toluene, 54%; **18** to **19a** : H_2, PtO_2, EtOH 99%, HOAc, 32%; then acetylation (100% **19b**) PCC, Celite, benzene, reflux, 18 h, 51% **20a**, hydrolysis, 5% NaOH in MeOH to **20b** then Jones, acetone, 0°C, 10 min, 100% **1a**.

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12 R.H.BURNELL and C.COTÉ. Synth. Commun. 18, 1753 (1988).

13 The procedure was adapted from Y.HE, H.M.CHANG, Y.K.LAU, Y.X.CUI, R.J.WANG, T.C.W.MAK, H.N.C.WONG and C.M.LEE. J. Chem. Soc., Perkin Trans 1, 3359 (1990). $AlCl_3$ (0.083 g) was suspended in dry 1,2-dichloroethane (0.8 mL) and cooled to 0°. Acetyl chloride (0.06 mL) was added followed by the substrate **21** (44 mg) in 1,2-dichloroethane (1 mL). The temp was allowed to rise to ambiant and stirring was continued overnight. The mixture was poured into ice/dil HCl and extracted with EtOAc. Evaporation of the well washed and dried organic phase and flash chromatography (silica gel 5% ether/pet.ether) gave **23a** (16 mg: 36%), m.p. 79-81°, $[\alpha]_D$ +58.5 (c, 0.60 $CHCl_3$): uv λ_{max} EtOH 257(25 500) and 319(8 300)nm; ^{1}Hmr δ: 0.93, 0.95 and 1.19 (3s, 3H each, Me at C.4 and C.10), 2.57 (s, 3H, CO-Me), 2.91 (dd, 1H, J = 8.8 and 1.5 Hz, H-C.5), 3.86 (s, 3H, MeO), 6.82 (s, 1H, H-C.11) and 7.44 (s, 1H, H-C.14); mass m/z: 300 (M^+,100), 286(25), 285(83), 217 (37) 215(27) and 203(45). *Exact mass* calcd for $C_{20}H_{28}O_2$: 300.2089; found: 300.2074.
Continued elution gave the acetate **23c** (12 mg: 25%) and then the phenol **23b** (5 mg: 12%). Since both of these are efficiently transformed to **23a**, the effective yield of the 13-acetyl product is over 70%.

(Received in USA 30 April, 1992)