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Synthesis of Natural Products from the Indian Neem Tree *Azadirachta indica*

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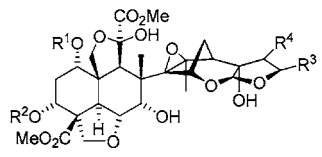
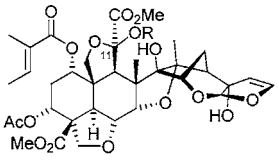
ABSTRACT



	R^1	R^2	R^3	R^4
3 vepaol	Tig	Ac	β-OMe	H
7 isovepaol	Tig	Ac	α-OMe	H
6 azadirachtin	Tig	Ac	═	
14 3-desacetylazadirachtin	Tig	H	═	



9 1-tigloyl-3-acetylazadirachtinin R = H
10 1-tigloyl-3-acetyl-11-methoxyazadirachtinin R = Me

The synthesis of five natural products (3, 6, 7, 10, and 14), isolated from the Indian neem tree *Azadirachta indica*, is reported from a common intermediate (2). The judicious choice of transacetalization conditions allows efficient access to both the azadirachtinin (9 and 10) and the azadirachtin (3, 6, 7, and 14) skeletons.

The neem tree, *Azadirachta indica*, is a large, fast-growing evergreen, prevalent in arid regions of the Indian subcontinent. The remarkable properties of this tree have been exploited for centuries, both to protect crops from insect pests and to treat ailments including hypertension, leprosy, and malaria.[1,2] The activity of neem extract[3] against insect pests can be primarily ascribed to the presence of azadirachtin **6**, which possesses powerful antifeedant[4] and growth disruptant properties.[5]

Although azadirachtin was first isolated in 1968,[4] its precise chemical structure was not elucidated until many years later.[6−8] More than 100 related compounds have since been isolated from the neem tree, and these can be assigned to one of three groups: azadirachtols, azadirachtins, and meliacarpins (Figure 1).[2] Compounds belonging to the azadirachtol or meliacarpin families lack the 11-OH or 4-CO_2Me groups, respectively, both of which are characteristic of the azadirachtins.

The first synthesis of azadirachtin (**6**) has recently been disclosed following 22 years of research within our laboratories.[9,10] Using the flexible route developed for this purpose, it was envisaged that other members of the azadirachtin family should be accessible from a common intermediate, namely epoxide **2**.[11]

In order to prepare **2**, tetrasubstituted olefin **1**[10] was first subjected to magnesium monoperoxyphthalate (MMPP),[12]

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(1) Mordue, A. J.; Blackwell, A. *J. Insect Physiol.* **1993**, *39*, 903−924.
(2) Schmutterer, H. *The Neem Tree*; Wiley-VCH: Weinheim, 1995.
(3) Extracts from the leaves, fruits, and seeds have all been used in crop protection; see ref 2.
(4) Butterworth, J. H.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1968**, 23−24.
(5) Schmutterer, H.; Rembold, H. *Angew. Entomol.* **1980**, *89*, 179−188.
(6) Turner, C. J.; Tempesta, M. S.; Taylor, R. B.; Zagorski, M. G.; Termini, J. S.; Schroeder, D. R.; Nakanishi, K. *Tetrahedron* **1987**, *43*, 2789−2803.
(7) Bilton, J. N.; Broughton, H. B.; Jones, P. S.; Ley, S. V.; Lidert, Z.; Morgan, E. D.; Rzepa, H. S.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1987**, *43*, 2805−2815.
(8) Kraus, W.; Bokel, M.; Bruhn, A.; Cramer, R.; Klaiber, I.; Klenk, A.; Nagl, G.; Pohnl, H.; Sadlo, H.; Vogler, B. *Tetrahedron* **1987**, *43*, 2817−2830.
(9) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Ayats, C.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7633−7635.
(10) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629−7632.
(11) Following our recent disclosure (see ref 2), it is now available via both total synthesis (see ref 10) and by degradation of the natural product (see ref 9).

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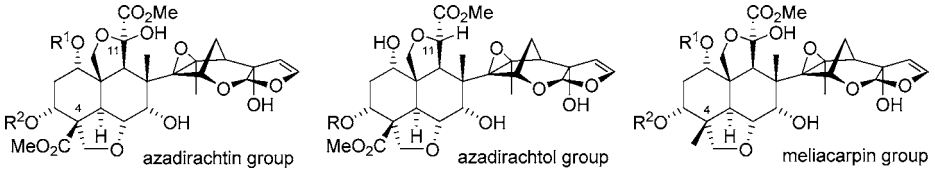
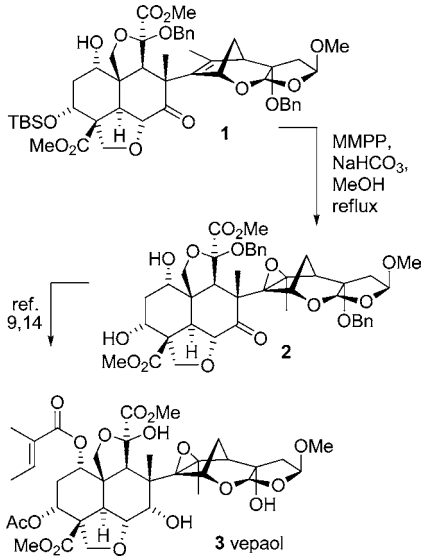


Figure 1. Three groups of natural products isolated from the neem tree.[2]

which effected the desired epoxidation reaction.[13] Following a modified workup procedure, employing NaOH in place of $NaHCO_3$, silyl ether cleavage was also achieved to provide **2** in an optimized yield of 80% over the two steps (Scheme 1). Subsequent steps[9,14] afforded vepaol **3**, identical in all

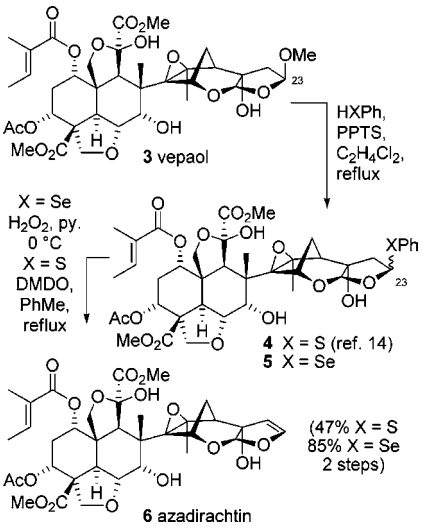
Scheme 1. Synthesis of Vepaol



respects to the natural product.[15,16]

We have also reported the conversion of **3** to azadirachtin (**6**), which was accomplished in a modest yield of 47% over two steps (X = S, Scheme 2).[9,14] This low yield was attributed to the high temperatures required to install the double bond in **6** via syn elimination of the intermediate sulfoxide (derived from **4**). Consequently, we anticipated that the use of benzene selenol to form the analogous selenoacetal (**5**) would circumvent this problem.

Scheme 2. Synthesis of Azadirachtin from Vepaol



Indeed, we were pleased to find that the yield of **6** could be increased to 85% over two steps under these optimized conditions. Thus, treatment of **3** with benzene selenol and pyridinium *p*-toluenesulfonate effected clean conversion to the selenoacetal (**5**) which, upon oxidation, led to spontaneous elimination of benzeneselenenic acid to yield azadirachtin (**6**).[4]

Isovepaol[17] (**7**), the C-23 epimer of vepaol, was then prepared from azadirachtin via a methoxybromination/reduction sequence employing *N*-bromosuccinimide in methanol followed by azo-bisisobutyronitrile and tributyltin hydride in toluene. The resulting mixture of **7** and **3** was separated, and the α-epimer proved to be identical to the natural product (**7**) (Scheme 3).[18]

During studies of the C-23 trans-acetalization (**3** to **4**) en route to azadirachtin (**6**) (vide supra), an unexpected product was isolated.[19] In addition to the desired acetal exchange, stronger acids were also able to promote intramolecular epoxide opening by the C-7 hydroxyl group in **3**. We sought

(12) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015−1017.

(13) Straightforward increase of the reaction time from 7 to 10 d, under identical conditions (cf. ref 10), led to improved conversion in the epoxidation of **1**. At this time, no further optimization has been performed for the epoxidation of 23-*epi*-**1**.

(14) Denholm, A. A.; Jennens, L.; Ley, S. V.; Wood, A. *Tetrahedron* **1995**, *51*, 6591−6604.

(15) Kraus, W.; Bokel, M.; Klenk, A.; Pohnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435−6438.

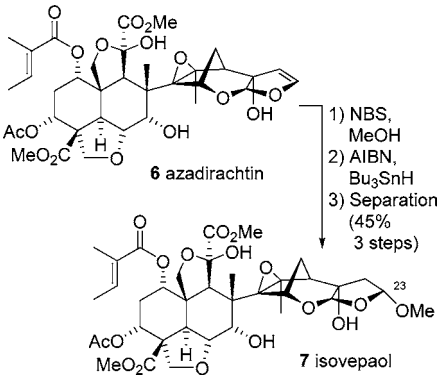
(16) The semisynthesis of **3** from azadirachtin has previously been reported; see: Ley, S. V.; Anderson, J. C.; Blaney, W. M.; Lidert, Z.; Morgan, E. D.; Robinson, N. G.; Simmonds, M. S. J. *Tetrahedron Lett.* **1988**, *29*, 5433−5436.

(17) Sankaram, A. V. B.; Murthy, M. M.; Bhaskaraiah, K.; Subramany, A. M.; Sultana, N.; Sharma, H. C.; Leuschner, K.; Ramaprasad, G.; Sitaramaiah, S.; Rukmini, C.; Rao, P. U. Natural Pesticides from the Neem Tree and Other Tropical Plants. In *Proc. 3rd Int. Neem Conf.* Schmutterer, H., Ascher, K. R. S., Eds.; Nairobi, Kenya, 1986.

(18) Although we have reported the conversion of **6** to an epimeric mixture of **3** and **7** previously (see ref 9), **7** was not separated for full characterization.

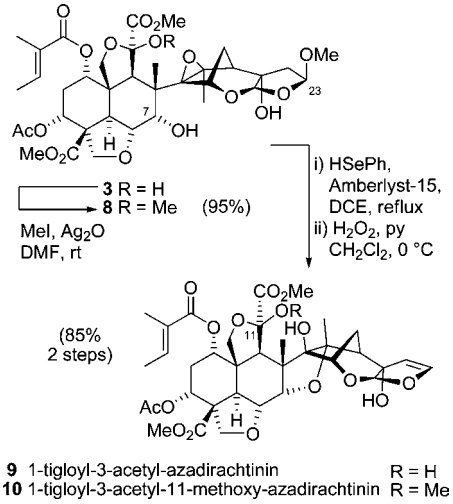
(19) Ley, S. V.; Anderson, J. C.; Blaney, W. M.; Jones, P. S.; Lidert, Z.; Morgan, E. D.; Robinson, N. G.; Santafianos, D.; Simmonds, M. S. J.; Toogood, P. L. *Tetrahedron* **1989**, *45*, 5175−5192.

Scheme 3. Synthesis of Isovepaol



to exploit this rearrangement in the preparation of the natural product 1-tigloyl-3-acetyl-azadirachtinin **9** (Scheme 4).[20]

Scheme 4. Synthesis of Azadirachtinins **9** and **10**



Although **9** had been prepared previously within our group by semisynthesis,[19] at that time it was not reported as a natural product. In 1996, Kumar[20] reported the isolation of **9** from neem extract, and we therefore examined an improved synthesis from **3**. Treatment of **3** with benzene selenol and sulfonic acid resin cleanly effected rearrangement of the azadirachtin skeleton and concomitant acetal exchange. The resulting epimeric selenides were immediately reacted with hydrogen peroxide/pyridine and underwent oxidation followed by syn elimination within 5 min at 0 °C to give 1-tigloyl-3-acetylazadirachtinin as a 3:1 epimeric mixture at C-11 (**9**). While we are confident in the assignment of synthetic material prepared, the NMR data differs substantially from that reported previously.[20] We can only therefore conclude that the natural product these authors isolated was not 1-tigloyl-3-acetylazadirachtinin but a closely related compound whose identity is currently unknown.[21]

(20) Kumar, C. S. S. R.; Srinivas, M.; Yakkundi, S. *Phytochemistry* **1996**, *43*, 451−455.

It was envisaged that another natural product, 1-tigloyl-3-acetyl-11-methoxyazadirachtinin[8] **10**, could be prepared via an analogous approach. Installation of the requisite methyl acetal at C-11 was followed by selective C-23 acetal exchange and skeletal rearrangement (Scheme 4). Finally, oxidation/elimination proceeded smoothly to furnish **10** in excellent yield for the first time,[22] with spectral data identical to that of the natural compound isolated by Kraus.[8] Alternative strategies to prepare this natural product from either azadirachtin (**6**) or 1-tigloyl-3-acetylazadirachtinin (**9**) proved unsuccessful.[23]

Efforts were now directed toward the synthesis of 3-desacetylazadirachtin (**14**).[24] Accordingly, our common intermediate (**2**) was first converted to diol **11** (Schemes 1 and 5). It was then necessary to temporarily protect the more reactive C-3 hydroxyl group in **11** as the corresponding acetate, thereby permitting installation of the C-1 tiglate group. The C-3 acetate could then be cleanly and selectively removed via methanolysis.

During the synthesis of 3-desacetylazadirachtin (**14**), it was necessary to effect a diastereoselective reduction of the C-7 carbonyl group in **12** to provide the axial alcohol required for the natural product (**14**). In the case of azadirachtin (**6**), which differs only by the presence of a tigloyl ester at C-1, the inherent reactivity of the system provides a 1:1 dr, employing cerium trichloride and sodium borohydride in methanol.[14] We were therefore surprised to find that under identical conditions, ketone **12** underwent selective reduction to the desired axial alcohol **13** in excellent yield (91%) with exclusive diastereoselectivity.

Cleavage of the benzyl ether of **13** proceeded without incident, and all that remained was the introduction of the enol ether present in the natural product. Acetal exchange followed by an oxidation/elimination protocol completed the synthesis of 3-desacetylazadirachtin (**14**), which was identical in all respects to the natural product.[24,25]

In summary, we have successfully prepared five natural products isolated from the Indian neem tree from a common precursor (**2**).[26] The use of a selenoacetal to install the

(21) Diastereomerically pure **9** underwent immediate epimerization when dissolved in buffered $CDCl_3$, which was not observed for the natural product. This, combined with the significant difference between NMR spectra, has led us to conclude that the two compounds are different.

(22) The synthesis of this compound has been reported in error, and we would like to thank the reviewer for pointing out this misprint; see: Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1993**, *10*, 109−157. In this reference, the compounds **52**/**53** depicted on p 117 should be the corresponding C-11 hemiacetals.

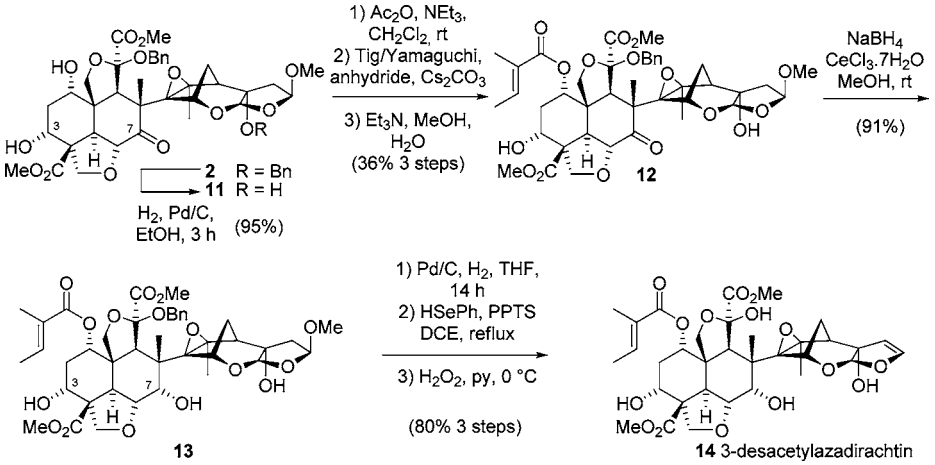
(23) Although selective C-11 methylation of azadirachtin (**6**) can be achieved, attempts to then induce skeletal rearrangement led to decomposition. In the case of 1-tigloyl-3-acetylazadirachtinin (**9**), it was not possible to effect C-11 methylation.

(24) Kraus, W.; Bokel, M.; Schwinger, M.; Vogler, B.; Soellner, R.; Wendisch, D.; Steffens, R.; Wachendorff, U. *Phytochemistry and Agriculture*; Oxford University Press: Oxford, 1993.

(25) It is worthy of note that **14** has been prepared previously from azadirachtin; see: Butterworth, J. H.; Percy, G. R.; Morgan, E. D. *J. Chem. Soc., Perkin Trans.* **1972**, *1*, 2445−2450. Yamasaki, R. B.; Klocke, J. A. *J. Agric. Food Chem.* **1987**, *35*, 467−471.

(26) We are confident that these compounds are correctly assigned as natural products and are not artifacts of isolation since treatment of azadirachtin with methanol under the isolation conditions (see ref 8) gave no trace of either **3** or **7**. Similarly, **9** showed no conversion to **10** under the isolation conditions; see ref 8.

Scheme 5. Synthesis of 3-Desacetylazadirachtin



reactive enol ether, prevalent throughout the neem natural products, offers several benefits including an increased yield and the possibility to access the azadirachtinin skeleton. With the exception of azadirachtin, these natural products are only isolated in trace amounts from neem extract,[8] and thus, by semisynthesis we have access to significant amounts of material for further biological evaluation. This clearly demonstrates the flexibility of our route developed for the synthesis of azadirachtin.

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Supporting Information Available: Spectra and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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