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Highly Selective Entry to the Azadirachtin Skeleton via a Claisen Rearrangement/Radical Cyclization Sequence

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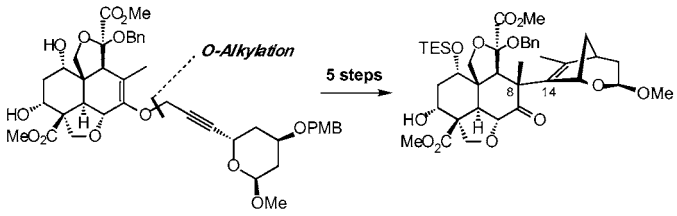
ABSTRACT



A highly diastereoselective, microwave-induced Claisen rearrangement of an appropriately substituted propargylic enol ether allows the formation of the sterically congested C_8–C_{14} bond of azadirachtin. When combined with a radical-mediated cyclization of the corresponding allene, this sequence offers rapid entry to the framework of azadirachtin.

Azadirachtin **1**, one of the most structurally complex and highly oxygenated triterpenoid isolates from the Indian neem tree *Azadirachta indica* (A. Juss) Meliaceae,[1] has gained considerable attention as a potential nontoxic, biodegradable, and natural pesticide.[2] However, the utility of this potent insect antifeedant[3] is limited by its instability in the field as a result of its propensity to undergo complex, irreversible rearrangements under mild acidic, basic, and photolytic conditions.[2b,4] Furthermore, the biochemical mode of action of azadirachtin remains unknown.[5] To address these issues, we have undertaken detailed biological and chemical studies on **1**;[2b] a flexible route to the total synthesis of this natural product that allows the development of analogues for biological screening is part of this program. Azadirachtin is a particularly challenging synthetic target by virtue of its 16 contiguous stereogenic centers, 7 tetrasubstituted carbons, and array of differentiated oxygen functionality. Additionally, three intramolecular hydrogen bonds have been proposed to hold **1** in a highly rigid conformation,[6] and the close proximity of so much restricted functionality renders the chemistry of azadirachtin subject not only to the inherent reactivity of the constituent groups but also to more poorly understood synergistic effects. The combination of these

(1) Butterworth: J. H.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1968**, 23−24.

(2) For reviews on the biological profile and previous synthetic studies on azadirachtin, see: (a) Ley, S. V. *Pure Appl. Chem.* **1994**, *66*, 2099−2102. (b) Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1993**, 109−157.

(3) Munakata, K. *Pure Appl. Chem.*, **1975**, *42*, 57. An *insect antifeedant* is defined as a substance that inhibits feeding but does not kill the insect directly, with death occurring consequently by starvation.

(4) (a) Johnson, S.; Morgan, E. D.; Wilson, I. D.; Spraul, M.; Hofmann, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, *11*, 1499−1502. (b) Ley, S. V.; Anderson, J. C.; Blaney, W. M.; Lidert, Z.; Morgan, E. D.; Robinson, N. G.; Santafianos, D.; Simmonds, M. S. J.; Toogood, P. L. *Tetrahedron* **1989**, *30*, 5175−5192. (c) Bilton, J. N.; Jones, P. S.; Ley, S. V.; Robinson, N. G.; Sheppard, R. N. *Tetrahedron Lett.* **1988**, *29*, 1849−1852.

(5) Several mechanisms, in addition to antifeedancy, include growth inhibition, malformations, and ecdysis inhibition; see: Schmutterer, H.; Rembold, H. *Z. Angew. Entomol.* **1980**, *89*, 179. For structure−activity relationship studies, see: (a) de la Puente, M. L.; Grossman, R. B.; Ley, S. V.; Simmonds, M. S. J.; Blaney, W. M. *J. Chem. Soc., Perkin. Trans. 1* **1996**, 1517−1521. (b) Ley, S. V.; Anderson, J. C.; Blaney, W. M.; Morgan, E. D.; Sheppard, R. N.; Simmonds, M. S. J.; Slawin, A. M. Z.; Smith, S. C.; Williams, D. J.; Wood, A. *Tetrahedron* **1991**, *44*, 9231−9246.

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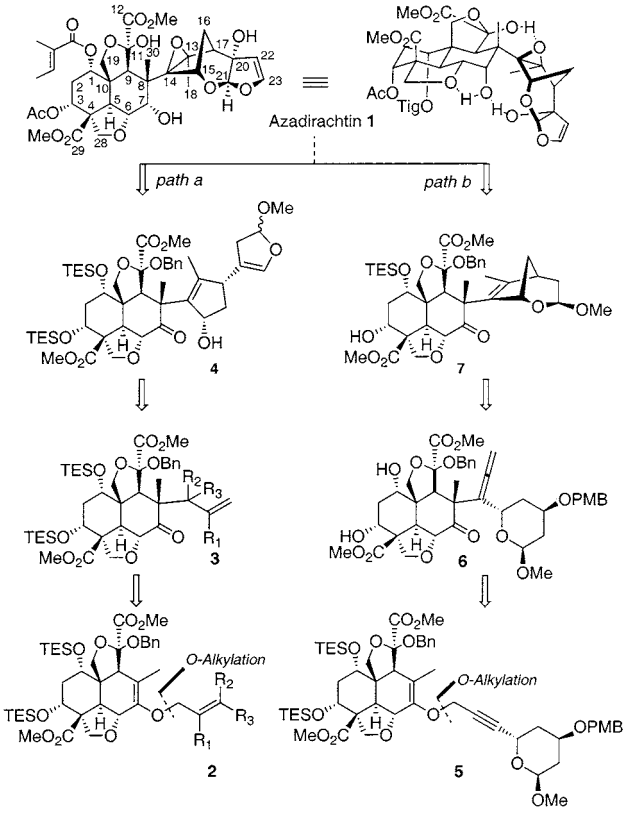
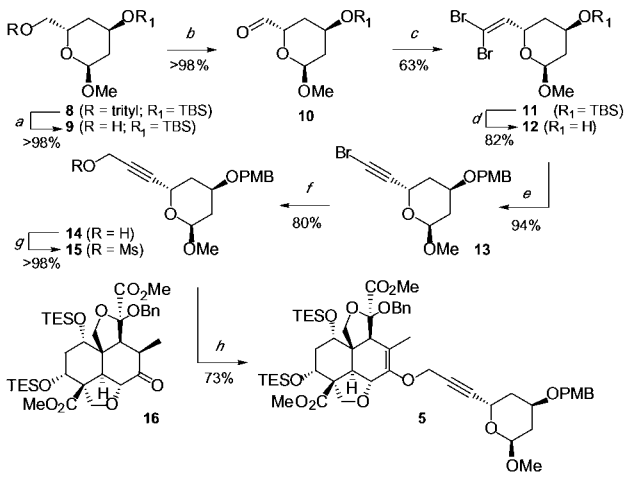
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) Na, NH_3, Et_2O, −78 °C, >98%; (b) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, >98%; (c) PPh_3, CBr_4, Zn, CH_2Cl_2, 22 °C, 63%; (d) HF_{aq} (48%), MeCN, 22 °C, 82%; (e) NaH, THF, NaI, PMBCl, 0 °C, 94%; (f) BuLi, THF, − 78 to 0 °C, then $(CH_2O)_n$, 80%; (g) Ms_2O, DIPEA, CH_2Cl_2, 0 °C, >98%; (h) NaH, THF, **16** (0.2 equiv relative to **15**), −78 °C, 73%, 65% recovered **15**.

factors is responsible for the lack of a total synthesis of **1** to date, despite significant attempts by the synthetic community.[7] In an earlier communication, we reported on the potential of using a Claisen rearrangement of simple allylic enol ethers such as **2** as a means of generating the C_8-C_{14} bond (Scheme 1, *path a*)[8] that we have found resistant to more direct, intermolecular coupling methods due to the extreme steric hindrance at this site.[9] Unfortunately, attempts to increase the complexity of the pendant allyl groups consistently resulted in inhibition of the critical rearrangement process, thus obviating the use of this route to install the tetracyclic right-hand portion of **1** in a single operation.

Furthermore, elaboration of such simple rearrangement products as **3** into the final azadirachtin skeleton through a biomimetic sequence initiated from **4** would be costly in terms of overall synthetic convergence. Here, we report a method for generating an advanced intermediate **7** by way of a microwave-assisted Claisen rearrangement[10] of the corresponding *propargylic* enol ether **5**; appropriate substitution of this precursor allows subsequent radical cyclization to form the bicyclo[3.2.1] ring system present in azadirachtin in a more rapid way (Scheme 1, *path b)* than is possible with the allylic enol ether systems (i.e. **2**).[11]

On the basis of the above considerations, we elected to prepare the substituted pyran **15**. The coupling of **15** onto the known Decalin ketone **16**[12] would set up the Claisen rearrangement and then by functional group manipulation provide access to an appropriate substrate for the radical cyclization. **15** was prepared in seven steps in 37% overall yield, starting from trityl protected alcohol **8** (Scheme 2).[13] Selective deprotection under reductive conditions, Swern oxidation, and Corey−Fuchs olefination[14] of the unstable aldehyde provided the dibromoalkene **11**. Subsequent silyl removal with aqueous HF occurred in 82% yield and was

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(7) (a) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2107−2110. (b) Nicolaou, K. C.; Follmann, M.; Roecker, A. J.; Hunt, K. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2103-2106. (c) Yamamoto, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Synthesis* **2000**, *13*, 1894−1906. (d) Watanabe, H.; Watanabe, T.; Mori, K.; Kitahara, T. *Tetrahedron Lett.* **1997**, *38*, 4429−4432. (e) Scheliger, H.; Winterfeldt, E. *Chirality* **1997**, *9*, 454−458. (f) Henry, K. J., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128−5129. (g) Chen, X. T.; Luo, Y. L.; Zhu, Q. B.; Wang, Z. Q. *Chin. Chem. Lett.* **1992**, *3*, 971−974. (h) Kenji, M.; Watanabe, H. *Chemistry* **1989**, *44*, 68−69. (i) Nisikimi, Y.; Iimori, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3354−3359. Added in proof: Fukuzaki, T.; Kobayashi, S.; Hibi, T.; Ikuma, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett.* **2002**, *4*, 2877−2880.

(8) Ley, S. V.; Gutteridge, C. E.; Pape, A. R.; Spilling, C. D.; Zumbrunn, C. *Synlett* **1999**, *8*, 1295−1297.

(9) Koot, W.-J.; Ley, S. V. *Tetrahedron* **1995**, *51*, 2077−2090.

(10) (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403−10432. (c) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665−1695.

(11) Elaboration to the 2,4-dioxatricyclo[6.2.1.0]undecane acetal by epoxidation and dihydroxyfuran ring formation remains a focus of our ongoing research. For a similar synthesis on a model system, see: Anderson, J. C.; Ley, S. V. *Tetrahedron Lett.* **1990**, *31*, 431−432.

(12) (a) Ley, S. V.; Lovell, P. J.; Slawin, A. M. Z.; Smith, S. C.; Williams, D. J.; Wood, A. *Tetrahedron* **1993**, *49*, 1675−1700. (b) Kolb, H. C.; Ley, S. V. *Tetrahedron Lett.* **1991**, *32*, 6187−6190.

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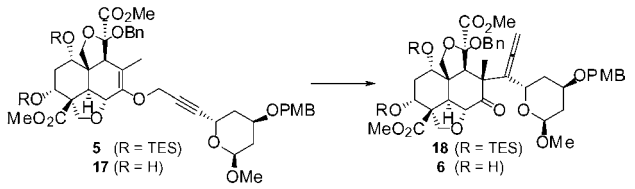
(14) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.

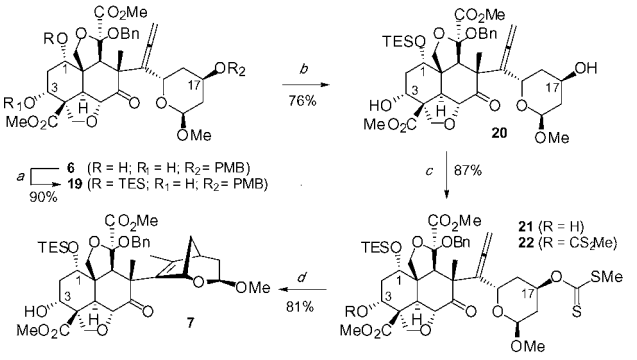
Table 1. Claisen Rearrangement Studies



entry	subst	temp, °C	conditions	prod	yield
1	**5**	180	DCB, 48 h	**18**	7
2	**5**	180	DCB, ***MWI***, 1 h	**18**	25
3	**17**	180	DCB, ***MWI***, 15 min	**6**	71[a]
4	**17**	180	DCB, ***MWI***, 15 × 1 min	**6**	88[b]

[a] Transformation was capricious, with decomposition often observed. [b] Employed 60-s microwave pulses instead of continuous irradiation (DCB = 1,2-dichlorobenzene; ***MWI*** = microwave irradiation).

Scheme 3 [a]



[a] Reagents and conditions: (a) TESOTf, DIPEA, −78 °C, 90%; (b) DDQ, CH_2Cl_2, H_2O, 0 °C, 76%; (c) NaH, CS_2, MeI, THF, −78 to −10 °C, 87%; (d) Bu_3SnH, AIBN, toluene, 110 °C, 81%.

followed with efficient alkyne formation and *p*-methoxybenzyl protection as a two-step, single-vessel transformation. Finally, condensation of **13** with $(CH_2O)_n$ and mesylation of the primary alcohol yielded the target pyran as a clear oil. *O*-Alkylation proceeded without incident only in the presence of sodium hydride and a 5-fold excess of **15**; gratifyingly, it was found that the unreacted mesylate could be recovered by chromatography and reused through at least four iterations without decomposition.[15]

Unfortunately, repeated attempts to induce the Claisen rearrangement of **5** resulted in near complete recovery of the starting material (Table 1, entries 1 and 2). We quickly decided on the basis of molecular models that the bulky silyl groups attached to the C_1 and C_3 alcohols may have created a sterically congested environment proximal to the reacting constituents. Thus, these groups were removed in 83% yield by treatment with TBAF and **17** was correspondingly subjected to thermal rearrangement conditions. Addition of a variety of Lewis acids known to promote Claisen rearrangements,[16] including $^iBu_3Al$,[17] Et_2AlSPh,[17] $TiCl_4$,[18] $BF_3{\cdot}Et_2O$,[19] NH_4Cl,[20] and $Yb(OTf)_3$,[21] were all unsuccessful. Notably, the thermal stability of **17** is undermined by Et_2AlSPh, $TiCl_4$, and $BF_3{\cdot}Et_2O$, with decomposition occurring even at ambient temperature in the latter two cases. Faced with these results, we attempted to induce the desired rearrangement by use of microwave irradiation, noting the small increase in yield observed when **5** was reacted under these conditions (Table 1, entry 2).[10] To our delight, microwave heating[22] of a solution of **17** in 1,2-dichlorobenzene at 180 °C *after only 15 min resulted in a 71% yield of the desired allene, and as a single diastereoisomer* (Table 1, entry 3).[23] While pleased by this result, we quickly found this transformation to be capricious on scale-up, with decomposition of both starting material and allene observed. After extensive optimization studies, we found that irradiation carried out with 15 *consecutive* 60-s pulses allowed the formation of the allene, in 88% yield, in a highly reliable fashion (Table 1, entry 4).[24]

With the substituted allene **6** in hand, elaboration to the bicyclic framework found in azadirachtin was effected (Scheme 3). This necessitated the appropriate protection of all pendant hydroxyl groups except at C_{17} (azadirachtin numbering), which needed to be transformed into an appropriate masked methylene radical for cyclization onto the allene. Unfortunately, despite forcing conditions including large excesses of TESOTf and DIPEA, only one of the two Decalin alcohols could be protected, providing further evidence of the peculiar steric environment created by the azadirachtin scaffold. Nonetheless, we continued, hopeful that the inability to silylate the C_3 alcohol would also translate to lack of reactivity in generation of the radical precursor. For this, deprotection of the *p*-methoxybenzyl group generated **20**. After some experimentation, we decided upon use of a xanthate as an appropriate radical generator.[25] However,

(15) Performance of **15**, as defined by yield of **5** and recovered mesylate, does not depreciate with iterative use, although reaction times tend to increase when recycled material is employed: (round 1) 73%, 64% recovered **15**, 6 h; (round 2) 65%, 65% recovered **15**, 3.5 h; (round 3) 73%, 78% recovered **15**, 14 h; (round 4) 86%, 80% recovered **15**, 20 h.

(16) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 206−243.

(17) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985−3988.

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(21) Sharma, G. V. M.; Ilangovan, A.; Sreenivas, P.; Mahalingam, A. K. *Synlett* **2000**, *5*, 615−618.

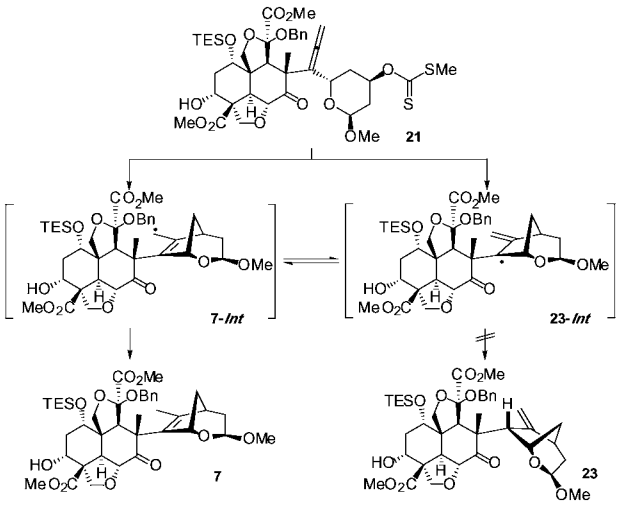
(22) A fully automated Coherent Synthesis System microwave machine was used. This was supplied by Personal Chemistry: Hamnesplanaden 5, 753 19 Uppsala, Sweden; www.personalchemistry.com.

(23) Stereochemistry was determined by nOe experiments and by comparison to a crystal structure obtained for an analogous compound (unpublished). See Supporting Information for full details.

(24) Reliability was determined by iterative transformation of 15 different samples of **17**. To date, we have never observed decomposition using these reaction conditions. Typical procedure: A 5-mL base-washed microwave vial was charged with **17** (9.50 mg, 0.012 mmol) and sealed. To the solid was added 1.0 mL of degassed 1,2-dichlorobenzene. The resultant mixture was subjected to 15 separate, 60-s microwave pulses, punctuated by 90-s cooling periods. After final cooling of the pale yellow solution, it was loaded onto a plug of silica gel and chromatographed with petroleum ether to remove the 1,2-dichlorobenzene, and subsequently EtOAc to remove the allene **6** (8.36 mg, 88%) as a white foam after solvent removal in vacuo. Attempts to scale this reaction have proceeded uneventfully.

(25) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672−685.

Scheme 4



after treatment with CS_2 and MeI under basic conditions, the *mono*-xanthate **21** and *bis*-xanthate **22** were isolated in equal quantities. Careful optimization of the reaction conditions followed the observation that **21** could be isolated in 87% yield with <5% of **22** generated if the reaction was stopped just prior to complete consumption of the starting diol.[26]

Although it was appreciated that thermodynamic quenching of the radical cyclization intermediate of **21** would yield the undesired *exo*-alkene **23**,[27] in practice, when **21** was treated with the radical initiator AIBN in the presence of a solution of Bu_3SnH in toluene at elevated temperature, *only the endo-alkene was formed* (Scheme 4). The most plausible rationale for this intriguing result rests upon the steric inaccessibility of tertiary radical **23-*Int***, which allows protonation only from **7-*Int***. Interestingly, no quenching of the initial methylene radical to produce the corresponding disubstituted allenyl pyran was observed,[28] indicating that closure onto the allene must be a facile event after radical generation.

In summary, the rapid entry to the coupled left- and right-hand skeletons present in azadirachtin has been achieved through a diastereoselective, microwave-assisted Claisen rearrangement and subsequent radical cyclization protocol. **7** bears a number of differentially protected reactive sites for further manipulation to derivatives not previously accessible,[29] and also to azadirachtin itself. Further studies to probe the generality of the key Claisen and radical cyclization steps, as well as further elaboration of this key intermediate, are ongoing and will be the subject of future correspondence from these laboratories.

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Supporting Information Available: Procedures and characterization for **5**−**7**, **9**−**15**, **17**, and **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) **22** was only observed to form after consumption of **20** was complete; thus, by immediate quenching of the reaction when <5% **20** remained, formation of the undesired bis-xanthate was circumvented.

(27) Sannigrahi, M.; Mayhew, D. L.; Clive, D. L. J. *J. Org. Chem.* **1999**, *64*, 2776−2788.

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(29) Neither the LHF nor the RHF alone have significant antifeedant activity. For previous SAR studies, see: (a) Blaney, W. M.; Simmonds, M. S. J.; Ley, S. V.; Anderson, J. C.; Toogood, P. L. *Entomol. Exp. Appl.* **1990**, *55*, 149. (b) Ley, S. V.; Santafianos, D.; Blaney, W. M.; Simmonds, M. S. J. *Tetrahedron Lett.* **1987**, *28*, 221−224.