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A Triple Diene-Transmissive Diels–Alder Strategy To Build the Quassinoid Framework

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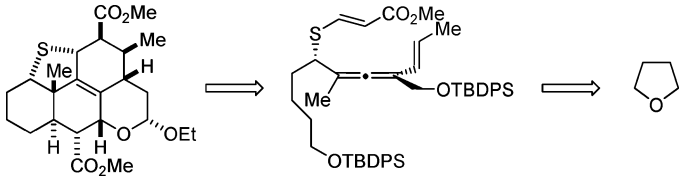
ABSTRACT



An advanced intermediate to the highly oxygenated triterpene quassinoids was prepared in 14 steps from tetrahydrofuran. The key steps are three diene-transmissive Diels–Alder cycloadditions. Several features of this synthesis are noteworthy, including a successful Mitsunobu reaction on an allenylic alcohol, a rare [4 + 2] cycloaddition involving an enethiol ether dienophile, and complete control over all 10 chiral centers created.

Quassinoids are degraded triterpenes isolated from the stem and bark of subtropical shrubs and trees belonging to the *Simaroubacea* species.[1,2] Their chemical synthesis is proving inordinately difficult as judged by the small number of successful syntheses (less than 20)[3] that were reported since the structure of the parent member, quassin (**1**), was published in 1960 (Figure 1).[4]

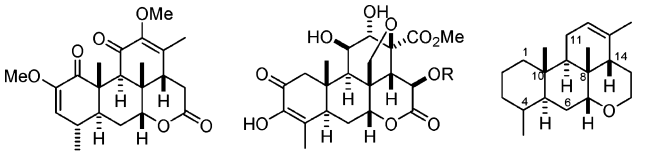


Figure 1. Quassinoids having the picrasane framework.

Their highly oxygenated carbon framework, of which bruceantin (**2**) is a typical example, and the large number of stereocenters they contain are the principal obstacles to their preparation in the laboratory. Besides the challenge they pose to synthetic chemists, efforts to prepare these compounds by synthesis is spurred by the large spectra of biological activities that many members of this family display (antiviral,

(1) For a review on the isolation and biological activities of quassinoids, see: (a) Guo, Z.; Vangapandu, S.; Sindelar, R. W.; Walker, L. A.; Sindelar R. D. *Curr. Med. Chem.* **2005**, *12*, 173−190. (b) Okano, M.; Fukamiya, N.; Lee K. H. *Stud. Nat. Prod. Chem.* **1990**, *7* (pt. A), 369−404. (c) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101−150. (d) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 221−264.

(2) For a review on the synthesis of quassinoids, see: (a) Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521−618. (b) Murae, T.; Sasaki M. *Stud. Nat. Prod. Chem.* **1992**, *11*, 71−111.

(3) For selected syntheses see: (a) Walker, D. P.; Grieco, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 9891−9892. (b) Grieco, P. A.; Collins, J. L.; Huffman J. C. *J. Org. Chem.* **1998**, *63*, 9576−9579. (c) Shing, T. K. M.; Jiang, Q. *J. Org. Chem.* **2000**, *65*, 7059−7069. (d) Hirota, M.; Yokoyama, A.; Miyaji, K.; Nakamura, H.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 435−438. (e) Stojanac, H.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853−855. (f) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504−511. (g) Shing, T. K. M.; Jiang, Q.; Mak, T. C. W. *J. Org. Chem.* **1998**, *63*, 2056−2057. (h) VanderRoest, J. M.; Grieco, P. A. *J. Org. Chem.* **1996**, *61*, 5316−5325. (i) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Igarashi, M.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 1119−1127. (j) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504−511. For a relay synthesis see: (k) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528−540.

(4) (a) Valenta, Z.; Gray, A. H.; Papadopoulos, S.; Podesva, C. *Tetrahedron Lett.* **1960**, *1*, 25−33. (b) Valenta, Z.; Gray, A. H.; Orr, D. E.; Papadopoulos, S.; Podesva, C. *Tetrahedron* **1962**, *18*, 1433−1441.

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antimalarial, antineoplastic, and antifeedant properties).[1] Recently reported biological activities suggest bruceantin should be reinvestigated for clinical efficacy against hematological malignancies, which has revived interest in this family of natural products with the hope that it will lead to a new therapeutic drug.[5]

Herein we report a highly efficient and stereoselective preparation of an advanced pentacyclic intermediate **3** possessing 18 of the 20 carbons of the so-called picrasane framework. The sequence encompasses three diene-transmissive Diels−Alder cycloadditions (**5** → **4** and **4** → **3** in Figure 2), each occurring with exquisite stereochemical control. This

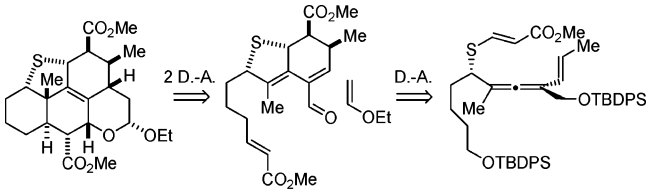
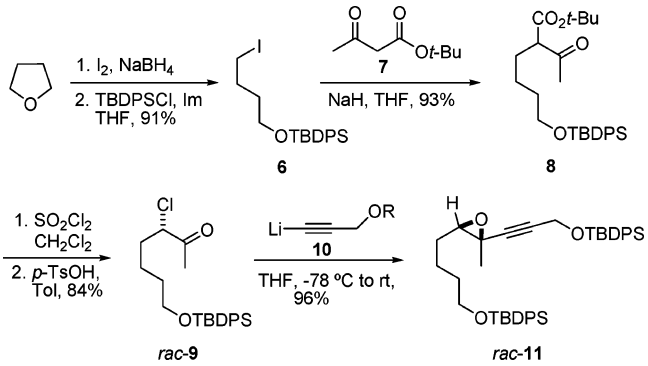


Figure 2. Retrosynthetic strategy to the picrasane framework.

strategy constitutes a significant improvement over a previous strategy, which involved only two diene-transmissive [4 + 2] cycloadditions, and importantly, the previous approach had failed to incorporate the C-10 methyl group (cf. Figure 1).[6]

The synthesis starts with the conversion of tetrahydrofuran to the protected iodobutanol **6**, which was used to alkylate the anion of *tert*-butylacetoacetate **7** to give **8** (Scheme 1).

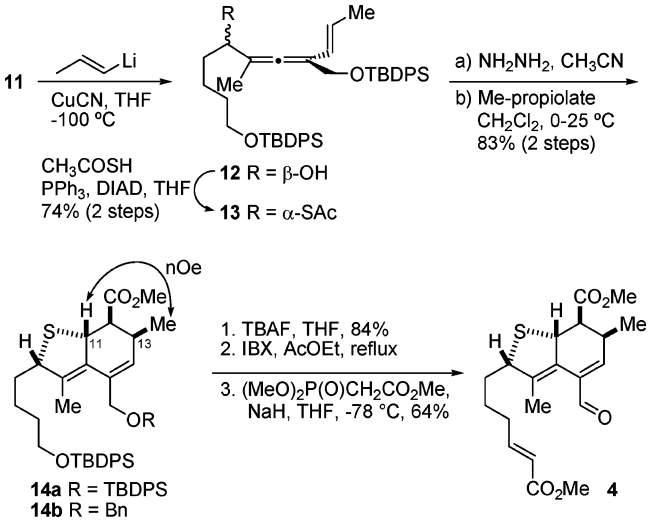
Scheme 1. Preparation of Propargylic Epoxide **11**



Chlorination of **8** followed by decarboxylation gave a racemic mixture of α-chloroketone **9**.[7] Addition of alkynyllithium **10** afforded a single diastereomer of epoxide **11** in 96% yield. The formation of the single isomer **11** is thought to arise from a completely stereoselective addition of the organolithium **10** to α-chloroketone **9** following the Felkin−Anh model of nucleophilic addition to carbonyls.[8]

Propargylic epoxide **11** was opened by a stereospecific S_N2' displacement using a higher order alkenylcyanocuprate prepared from propenyllithium to give the unstable vinylallene **12** (Scheme 2).[9]

Scheme 2. Preparation of Diene-Transmissive Precursor **4**



Its stereochemistry was inferred from the stereochemistry of a later intermediate (vide infra). Vinylallene **12** was submitted to the Mitsunobu reaction condition with thioacetic acid, giving the thioacetate **13** in 74% yield for the last two steps. To the best of our knowledge, only one Mitsunobu reaction on an allenic alcohol has been reported in the literature,[10] and it did not involve the use of a sulfur nucleophile.

The deprotection of the thiol in **13** was achieved in an unusual way using hydrazine hydrate,[11] and all attempts to isolate the corresponding thiol were unsuccessful. Consequently, coupling with methyl propiolate was performed without isolating the thiol, and the cycloaddition product **14a** was directly obtained in 83% yield for the overall conversion. The stereochemistry was assigned by analysis of the NOESY spectrum of a very close analogue (see **14b** in Supporting

(5) Cuendet, M.; Pezzuto, J. M. *J. Nat. Prod.* **2004**, *67*, 269−272.

(6) (a) Spino, C.; Hill, B.; Dubé, P.; Gingras, S. *Can. J. Chem* **2003**, *81*, 81−108. (b) Spino, C.; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596−5608.

(7) α-Chloroketones have been prepared in nonracemic form by the alkylation of chiral α-chloro imidates and offers the possibility of an asymmetric version of our synthesis. See: (a) Pridgen, L. N.; De Brosse, C. *J. Org. Chem.* **1997**, *62*, 216−220. (b) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39−42.

(8) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.

(9) For recent discussions on the mechanism of S_N2' cuprate displacements, see: (a) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287−6293. (b) Karlstrom, A.; Sofia, E.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 1981−1989. For selected examples involving alkylnyl epoxides, see: (c) Dieter, R. K.; Chen, N.; Yu, H.; Nice, L. E.; Gore, V. K. *J. Org. Chem.* **2005**, *70*, 2109−2119. (d) Fernández de la Pradilla, R.; Viso, A.; Castro, S.; Fernández, J.; Manzano, P.; Tortosa, M. *Tetrahedron* **2004**, *60*, 8171−8180.

(10) Ma, S.; Yu, F.; Gao, W. *J. Org. Chem.* **2003**, *68*, 5943−5949.

(11) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552−6554.

Information) where a NOE enhancement was observed between the C13 methyl group and the C11 proton (cf. Scheme 2). The stereochemistry of **14** is in line with the stereochemistry observed in other similarly prepared compounds.[6a,12] It arises from an *endo* transition state in which the enethiol-ester adopts the *E* geometry (Figure 3). It is

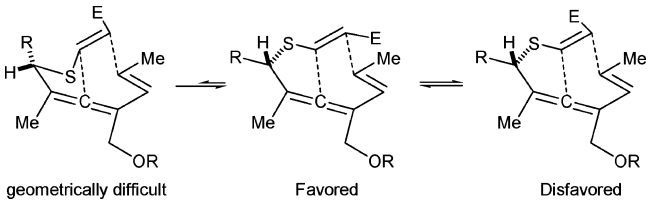


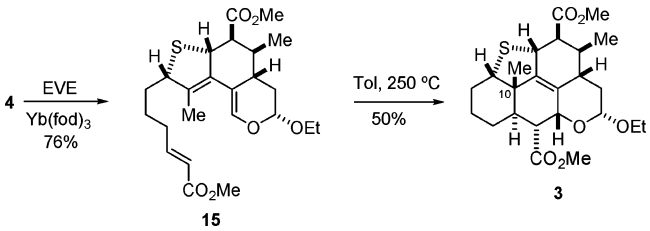
Figure 3. Transition states of the intramolecular cycloaddition giving **14**.

probable that the addition of the thiol to the propiolate ester is reversible but that the (*E*)-enethiol undergoes a faster cycloaddition. The enethiol intermediate was never detected during the reaction. The temperature at which this Diels–Alder reaction occurs is remarkably low (25 °C) thanks to an early transition state in which the severe steric interactions of the final product (between the vinylic methyl and CH_2-OR groups) are not yet present.[13]

Deprotection and oxidation with IBX[14] of both alcohols in **14a** gave a dialdehyde, which underwent a chemoselective olefination using the Horners–Wadsworth–Emmons conditions to afford compound **4** (Scheme 2). Only a trace of the diolefination product was detected under the conditions used, though exposure of the dialdehyde to an excess of the phosphonate reagent did result in higher amounts of this unwanted product being isolated.

The hetero-Diels–Alder cycloaddition of **4** and ethylvinyl ether (EVE) proceeded in very good yield (76%) and cycloadduct **15** was obtained as a single diastereomer (Scheme 3). The stereochemistry of **15** results from an *endo*

Scheme 3. Two Diels–Alder Cycloadditions for the Preparation of **3**



(12) Dubé, P. Ph.D. Thesis, Université de Sherbrooke, 2005.
(13) Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283–5287.
(14) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.

approach of ethylvinyl ether from the less hindered bottom face of oxadiene **4**, as expected (Figure 4, top).[6] Heating **15**

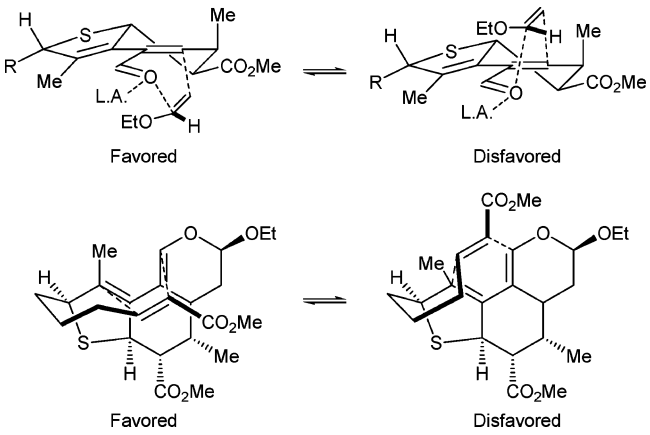


Figure 4. Transition states of the cycloadditions of **4** and **15**.

to 250 °C for 17 h resulted in the formation of only one pentacyclic adduct **3** in 50% yield. Careful analysis of the NOESY spectrum of **3** allowed us to unambiguously establish its stereochemistry, which was later confirmed by a single-crystal X-ray diffraction analysis of the sulfone derivative **16** (Figure 5), thus confirming the earlier stere-

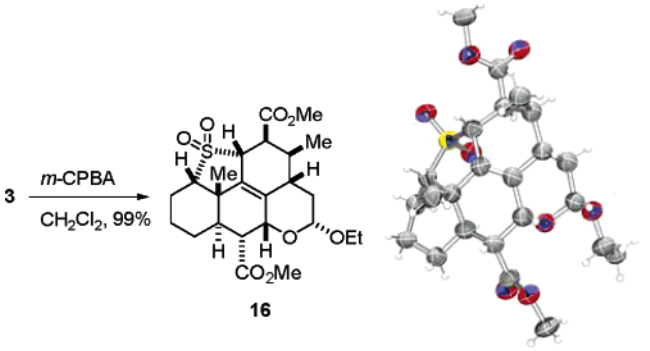
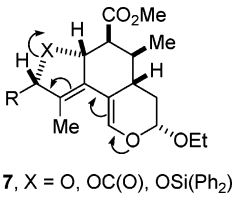


Figure 5. Oxidation of compound **3** and ORTEP diagram of the resulting sulfone **16**.

ochemical assignment of compounds **11** and **14**. We have not yet fully investigated the use of Lewis acids to lower the temperature at which the final cycloaddition takes place. The stereochemistry of **3** results from an *endo* chairlike transition state (Figure 4, bottom). It is interesting to note that when the C10 methyl group and sulfur linkage are absent, similar cycloadditions occur at 25 °C.[6]

The survival of the sulfide functionality to the reaction conditions of the hetero- and the intramolecular Diels–Alder reactions was welcome but somewhat unexpected in view of the fact that analogous oxygen functionalities do not

withstand such conditions.[6a,12] The main decomposition pathway for these compounds is depicted in Figure 6. The



17, X = O, OC(O), OSi(Ph_2)

Figure 6. Decomposition pathway of oxygen analogues of **15**.

presence of the sulfur atom in **3** will undoubtedly be useful to introduce the C8-carbon and further elaborate ring A.

In conclusion, the synthesis of the advanced pentacyclic intermediate **3** was achieved in only 14 steps from a very simple starting material and with complete control over the stereochemistry of all 10 stereogenic centers. The enethiol connector for the first Diels−Alder (**13** → **14a**) is a cornerstone of the synthesis in that the sulfur linkage controls the stereochemical outcome of both the first and third [4 + 2] cycloadditions. Efforts toward the total synthesis of natural quassinoids are continuing and will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, ^{1}H NMR spectra for all new compounds, and single-crystal X-ray analysis data for **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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