A Stereoselective Diene-Transmissive [4 + 2]-Cycloaddition Strategy for the Construction of the Tetracyclic Quassinoid Framework

Claude Spino* and Gang Liu

University of Victoria, Chemistry Department, P.O. Box 3055, Victoria, British Columbia, Canada V8W 3P6

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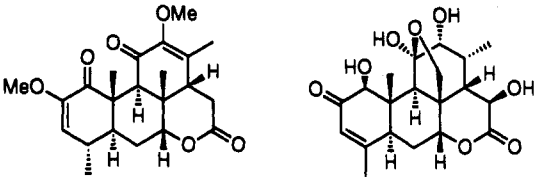
Summary: The tetracyclic quassinoid framework was stereoselectively constructed using a diene-transmissive Diels–Alder reaction between the cyclic formyl-diene **13** and ethyl vinyl ether.

The quassinoids form a large family of degraded triterpenes isolated from plants of the genus *Simabouraceae*.[1] Their wide range of biological activities, including antineoplastic, antiviral, antimalarial, and insect antifeeding properties, has spurred much interest in the research community in the last two decades. For the synthetic organic chemist, the quassinoids represent a formidable challenge.[2] Their complex array of stereocenters and the extent of oxygenation of their carbon skeleton combine to make their synthesis laborious. They have indeed resisted duplication until Grieco's synthesis of quassin (**1**) in 1980,[3] nearly 20 years after its structure



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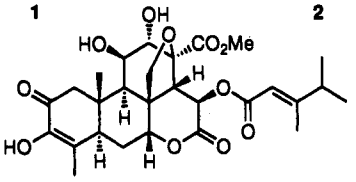

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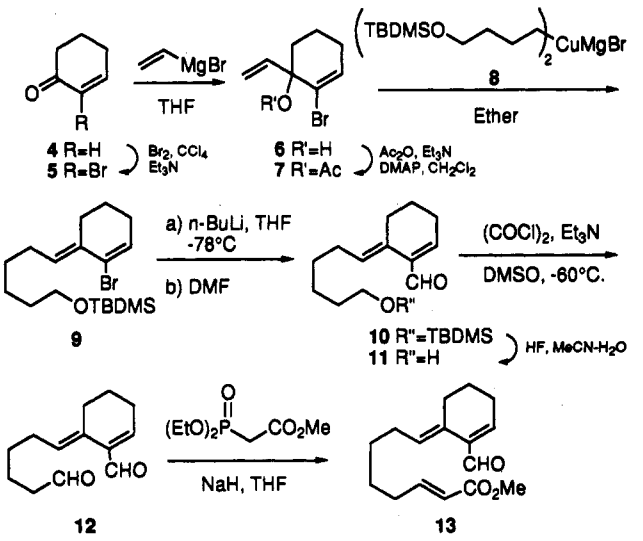
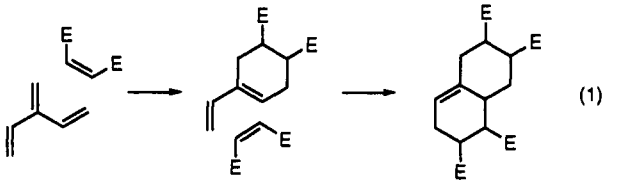
was elucidated.[4] Several quassinoids have been synthesized since,[5] including antileukemic glaucarubolone (**2**)[6] and bruceantin (**3**).[7] In our first contribution to this area, we describe an approach based upon a "diene-transmissive" Diels–Alder cycloaddition strategy. This strategy effectively and stereoselectively generates three rings and six chiral centers in a single step. In addition, the key reactions in this strategy should be compatible with many functional groups thus easing the synthetic design of quassinoids.

Scheme I



Although the diene-transmissive Diels-Alder reaction between the cross-conjugated triene 3-methylene-1,4-pentadiene and two dienophiles was described as early as 1955, this strategy has not been used to a significant extent in synthesis despite its apparent potential (eq 1).[8,9]



(1)

We envisaged that the tetracyclic framework of the quassinoids could be stereoselectively and efficiently prepared using a diene-transmissive Diels–Alder strategy where an initial intermolecular inverse electron-demand cycloaddition of a cyclic unsaturated aldehyde and an electron-rich dienophile would set up a second diene unit allowing a trans-selective, intramolecular Diels–Alder reaction to take place (cf. Scheme II). To test the feasibility of this approach we prepared the model compound **13** in eight steps from 2-cyclohexen-1-one (**4**) as described in Scheme I. Bromination–elimination of **4** gave the vinylic bromide **5**[10] (77%) which was reacted with vinylmagnesium

(1) For reviews, see: Polonsky, J. *Forts. Chem. Org. Naturst.* **1973**, *30*, 101; *Ibid.* **1985**, *47*, 221.

(2) For a review of synthetic routes to quassinoids, see: Kawada, K.; Kim, W.; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521.

(3) Grieco, P. A.; Ferriño, S.; Giovanni, V. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Giovanni, V.; Ferriño, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.

(4) Valenta, Z.; Gray, A. H.; Orr, D. E.; Papadopoulas, S.; Podesva, C. *J. Am. Chem. Soc.* **1962**, *90*, 1433.

(5) (a) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764. (b) Fleck, T. J.; Grieco, P. A. *Tetrahedron Lett.* **1992**, *33*, 1813. (c) Stojanac, N.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853. (d) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Igarashi, M.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 1119. (e) Gross, R. S.; Grieco, P. A.; Collins, J. L. *J. Am. Chem. Soc.* **1990**, *112*, 9436. (f) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528. (g) Collins, J. L.; Grieco, P. A.; Gross, R. S. *J. Org. Chem.* **1990**, *55*, 5816. (h) Grieco, P. A.; Nargund, R. P.; Parker, D. T. *J. Am. Chem. Soc.* **1989**, *111*, 6287. (i) Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron Lett.* **1989**, *30*, 5989. (j) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 435.

(6) Fleck, T. J.; Grieco, P. A. *Tetrahedron Lett.* **1992**, *33*, 1813.

(7) Relay synthesis of bruceantin: Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528.

(8) Blomquist, A. T.; Verdol, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 81. Bailey, J. W.; Economy, J. *J. Am. Chem. Soc.* **1955**, *77*, 1133. Bailey, W. J.; Cunov, C. H.; Nicholas, L. *J. Am. Chem. Soc.* **1955**, *77*, 2787.

(9) See, Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1198 and references cited therein. Motoki, S.; Matsuo, Y.; Terauchi, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 284.

(10) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.

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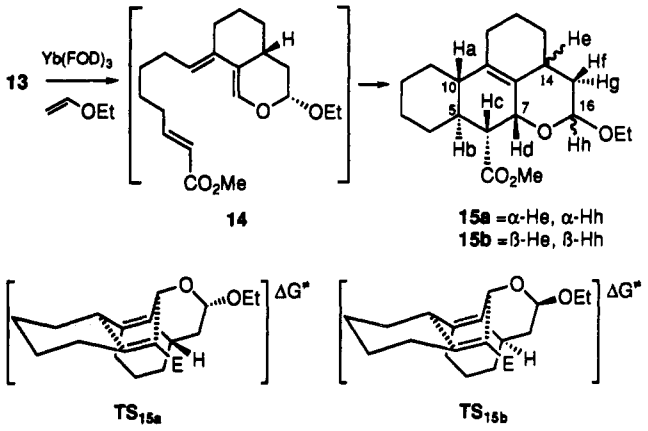
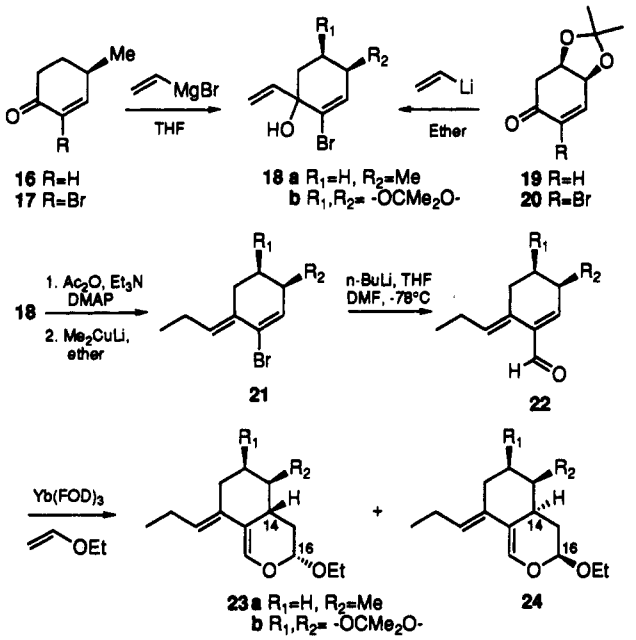
Scheme II



bromide to provide alcohol **6** in 73% yield. The acetate **7**, derived from **6** (79%), was regioselectively displaced, in a S_N2' sense, by the cuprate reagent **8**[11] to afford diene **9** as a single geometric isomer.[12] The lithium–halogen exchange reaction of **9** with *n*-butyllithium followed by trapping of the vinyl anion with dimethylformamide gave aldehyde **10** in 80% yield from the acetate. Removal of the silyl group with hydrofluoric acid proceeded in 92% yield to give **11** and was followed by an oxidation of the resulting primary alcohol using the Swern reaction conditions[13] to afford the dialdehyde **12** in 85% yield. The latter underwent a chemoselective Wadsworth–Emmons reaction with methyl diethylphosphonoacetate to give the desired *E*-α,β-unsaturated ester **13** in 87% yield.

The ytterbium-catalyzed,[14] inverse-electron demand, Diels–Alder cycloaddition between **13** and ethyl vinyl ether (as solvent) at room temperature was immediately followed by a stereoselective intramolecular Diels–Alder cycloaddition (IMDAC) to give the tetracyclic compounds **15a** and **b** in 87% yield in a 6:1 ratio (Scheme II).[15] The stereochemistry of the major cycloadduct **15a** was deduced from NOE experiments (positive enhancements between Ha–Hd, Hc–Hd (strong), Hd–Hf, Hg–Hh, and no enhancement between Hb and Hc) and from the coupling constants of Hc ($J_{Hb-c} = J_{Hc-d} = 9.3$ Hz). The minor isomer **15b** displays coupling constants for $J_{Hb-c} = 12.5$ Hz, $J_{Hc-d} = 6.5$ Hz, $J_{Hf-h} = 2.5$ Hz, and $J_{Hg-h} = 9.8$ Hz which are in agreement with the proposed structure (Hb–Hc must be trans-diaxial, so Hc–Hd are cis). Thus, both isomers have the same stereochemistry at C_5–C_{10}, arising from two chairlike transition states TS_{15a} and TS_{15b}, which is consistent with our predictions based on the literature.[16]

Scheme III



It should be possible to control the absolute stereochemistry of C_5–C_{10}, independently of C_{14}, by placing suitable chiral substituents on the acyclic chain in **13** that will adopt an equatorial position in the chairlike transition state of the IMDAC.[16] So we first investigated the control of the stereochemistry at C_{14} on the model aldehydes **22** which were synthesized using a route analogous to the preparation of compound **10** (Scheme III). Racemic enone **16** was prepared from *p*-methylanisole.[17] Bromination–elimination of **16** gave vinylic bromide **17** in 64% yield. Addition of vinylmagnesium bromide produced two isomeric alcohols **18a** in 84% yield. Acetylation (70%) followed by Sn2′ displacement of the resulting allylic acetate with lithium dimethylcuprate afforded a 72% yield of the *E*-exocyclic olefin **21a**. The metal–halogen exchange reaction was then used, as before, to obtain the desired aldehyde **22a** in 72% yield. Optically pure enone **19** was prepared in four steps from (−)-quinic acid[18] and was submitted to a similar sequence of reactions as with **16** to afford optically active aldehyde **22b** in a comparable overall yield. Note that the reaction of **20** with vinylmagnesium bromide gave predominantly the 1,4-addition product even in the presence of excess magnesium dibromide or anhydrous cerium trichloride.[19] Delivery of the reagent to the olefin by chelation to the isopropylidene oxygen is presumably the cause of this unexpected Michael addition. Reaction of **20** with vinyllithium in ether, on the other hand, gave a 53% yield of a single 1,2-addition product **18b** and traces of the 1,4-adduct.

The ytterbium-catalyzed cycloaddition of **22a** (R_1 = H, R_2 = Me) with ethyl vinyl ether gave a 3.5:1 mixture of inseparable stereoisomers **23a** and **24a** in 87% yield (GC analysis) (Scheme III). Unfortunately, we could not rely on the NOESY spectrum of **23a** to assign its stereochemistry because of overlapping resonances. However, we

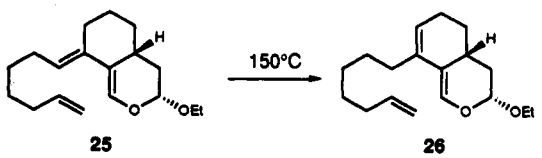
(11) The precursor to reagent **8** was prepared by protecting 4-bromo-1-butanol as its *tert*-butyldimethylsilyl ether (TBDMSOTf, Et_3N, CH_2Cl_2).

(12) Crabbé, P.; Dollat, J.-M.; Gallina, J.; Luche, J.-L.; Velarde, E. *J. Chem. Soc., Perkin Trans. 1* **1978**, 730.

(13) Mancuso, A. J.; Juang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(14) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721.

(15) Compound **25**, the analog of **14** lacking the activating ester group on the terminal olefin, undergoes a migration of the double bond inside the ring at high temperature, thus preventing the IMDAC.



(16) See examples of internally substituted trienes in: Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187 and references cited therein.

(17) Kwart, H.; Conley, R. A. *J. Org. Chem.* **1973**, *38*, 2011. The hydrolysis of 1-methoxy-4-methylcyclohexadiene was carried out in refluxing 6 N aqueous sulfuric acid.

(18) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738.

(19) $CeCl_3$ has been shown to favor the 1,2-addition of Grignard reagents to unsaturated carbonyls; see: Imamoto, I.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

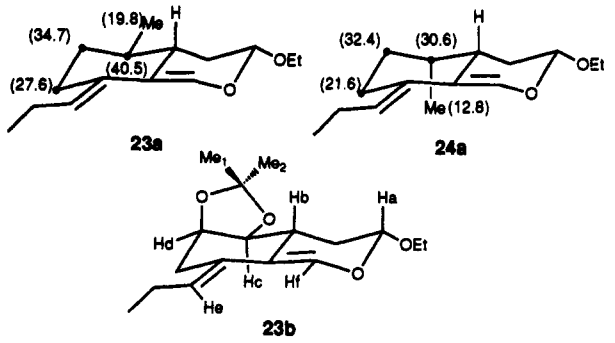


Figure 1. 3-D structures of **23a**, **23b**, and **24a**. Numbers in parentheses refer to ^{13}C NMR resonances. See text for discussion.

compared the ^{13}C NMR resonances of the major and minor isomers and found them to be consistent with structures **23a** and **24a**, respectively (Figure 1).[20] Cycloaddition of **22b** (R_1, R_2 = $-OCMe_2O-$) with ethyl vinyl ether gave a 66% pure yield of the desired cycloadduct **23b** and 12% of an inseparable 1:1 mixture of two compounds.[21] The stereochemistry of the adduct **23b** was unambiguously established from its ^1H NMR and NOESY spectra. Enhancements between Ha–Hb, Hb–Me_1, Hc–Hd, and He–Hf were proof of the proposed structure (Figure 1). As hoped, the methyl and acetonide substituents were able to direct the attack of the incoming ethyl vinyl ether to the opposite face of the molecule by steric hindrance. We believe that this stereoselectivity will increase when more elaborate dienophiles (substituted with oxygens at both carbons) are used. Cycloadduct **23b** is a particularly interesting model as it is optically active and contains useful functionalities for further elaboration of ring C in the quassinoids.

We are currently preparing more elaborate chiral analogs of **13** to achieve control on the absolute stereochemistry in the IMDAC reaction in an effort toward the total synthesis of natural quassinoids. We are also investigating the use of the diene-transmissive Diels–Alder reaction of cyclic trienes for the synthesis of other classes of natural products, such as the atisanes and amphilectanes.

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Supplementary Material Available: Experimental procedures and spectral data for compounds **5–24**, ^1H NMR spectra of **23a,b**, ^{13}C NMR spectra of **15a** and **23a**, COSY spectra of **15a**, NOE difference spectra of **15a**, and NOESY spectra of **15a** and **23b** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) See: Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. In *Tables of Spectra Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1989; pp C50–C65.

(21) No definite structures could be assigned to either minor isomers, though one of them could perhaps be **24b** based on proton NMR.