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Meldrum's Acid-Derived Thione Dienophile in a Convergent and Stereoselective Synthesis of a Tetracyclic Quassinoid Intermediate

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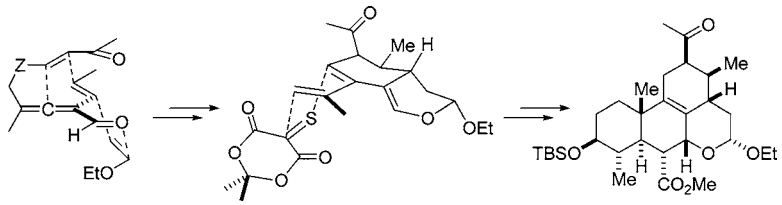
ABSTRACT



An advanced intermediate toward anti-cancer quassinoids has been synthesized using a quadruple diene-transmissive [4+2]-cycloaddition strategy. High convergence is achieved thanks to a regio- and stereoselective hetero-Diels–Alder reaction using a thione. The relative stereochemistry of the final Diels–Alder adduct was controlled by tethered substituents introduced via a highly syn- and γ-selective vinylogous Mukaiyama aldol.

Quassinoids, represented by quassin and bruceantin (Figure 1), form a large family of naturally occurring and biologically

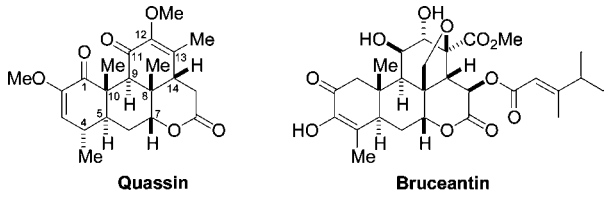


Figure 1. Representative quassinoids.

active molecules isolated as bitter principles of subtropical shrubs and trees of the *Simaroubaceae* genera.[1] These heavily oxygenated lactones are considered promising therapeutic agents, thanks to their wide spectrum of biological activities.[1,2] The majority of these degraded triterpenes possesses the same carbon skeleton as quassin, the so-called C20 picrasane framework (Figure 1). Despite the fact that over 300 quassinoids have been identified since 1960,[3] less than 20 completed total syntheses have been reported to date.[4]

Our basic strategy utilizes three diene-transmissive [4+2]-cycloadditions taking full advantage of the power of the Diels−Alder cycloaddition in building up molecular complexity with efficient stereochemical control (Scheme 1).[5,6]

(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., Part A* **1990**, *7*, 369−404. (c) Polonsky, J. *Chem. Org. Naturst.* **1973**, *30*, 101−150. (d) Polonsky, J. *Chem. Org. Naturst.* **1985**, *47*, 221−264.

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

(3) (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.

(4) For selected syntheses, see: (a) Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981−7984. (b) Grieco, P. A.; Collins, J. L.; Huffman, J. C. *J. Org. Chem.* **1998**, *63*, 9576−9579. (c) Stojanac, H.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853−855. (d) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Igarashi, M.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 1119−1127. (e) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504−511.

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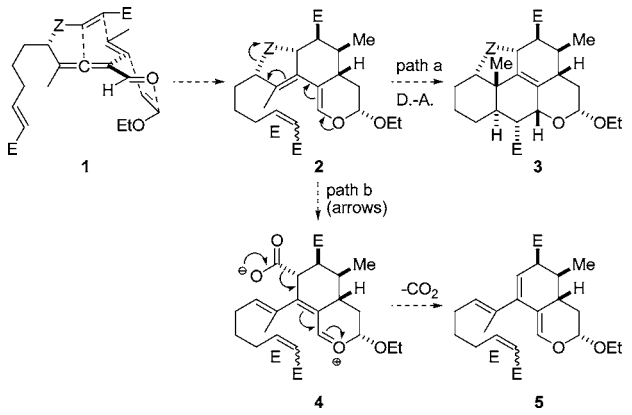
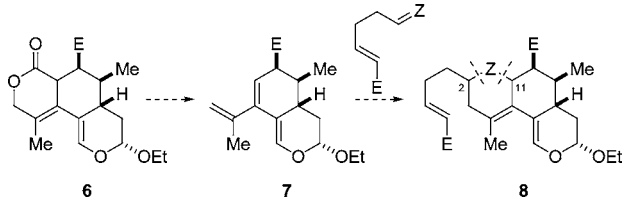
Scheme 1. Diene-Transmissive Diels−Alder Cycloaddition Strategy and Decarboxylation Pathway to Form Diene **5**



We have already demonstrated that, using a sulfur atom as a connector (Z = S in **2**), all three Diels−Alder reactions occur to give pentacyclic intermediate **3** (path a).[7] An interesting opportunity arose when a lactone (Z = O_2C in **2**) was used as a connector. The desired tetracyclic compound **3** was not formed, but we instead detected product **5**, which came from the decomposition of **2** according to path b.[5b]

At first glance, the decomposition of **2** into diene **5** seems like an unfortunate event. However, we imagined that it could be, in fact, a blessing in disguise. If this decomposition process could be optimized to give, for example, diene **7** (Scheme 2) and if yet another [4+2]-cycloaddition could be

Scheme 2. Retrosynthetic Analysis

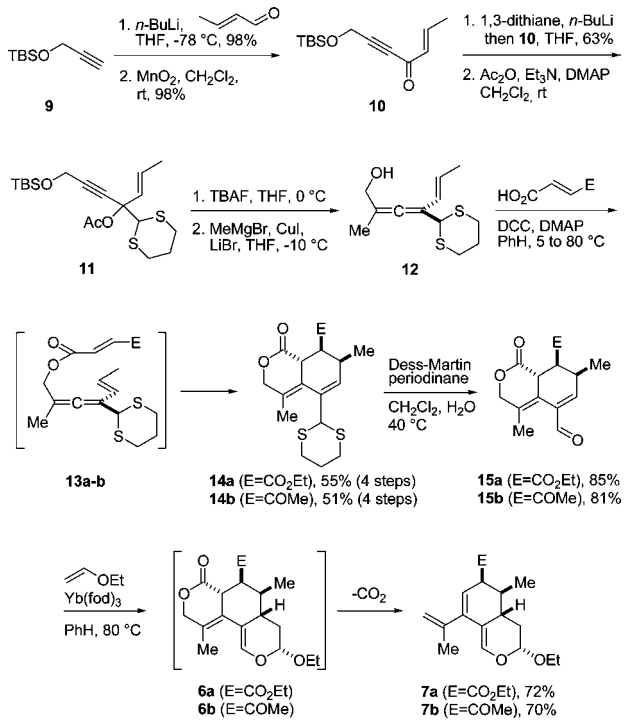


effected on diene **7**, it would bring in a large fragment of the molecule in a very convergent way while retransmitting the original diene unit found in compound **2**. Moreover, the sequence involves no extra step because the decomposition of **6** was effected during its formation (vide infra). To accomplish the final cycloaddition (Scheme 1, path a), the dienophile tether Z in **8** would have to be cleaved at C2 and/or C11.

We report herein the successful realization of this strategy involving four diene-transmissive Diels−Alder cycloadditions. The key feature of our approach is a remarkable regio- and stereoselective hetero-Diels−Alder reaction involving a Meldrum's acid-derived thione dienophile.[8]

We began with the synthesis of 1,3-dienes **7a**,**b**. The addition of the alkynyllithium derived from **9** to *trans*-crotonaldehyde gave an allylic alcohol that was oxidized and reacted with the anion of 1,3-dithiane to give **11** after acetylation of the tertiary alcohol (Scheme 3). Deprotection

Scheme 3. Stereoselective Synthesis of 1,3-Dienes **7a** and **7b**



of the primary alcohol followed by an S_N2' displacement of the acetate with a higher-order methylcuprate reagent led to vinylallene **12**, with no byproduct resulting from the addition on the double bond.[9]

Fumaric acid monoethyl ester or 4-oxo-2-pentenoic acid[10] was separately tethered to the primary alcohol using DCC in benzene. There was no need to isolate **13a** or **13b** because simply warming the reaction mixtures to 80 °C triggered a stereoselective intramolecular Diels−Alder cycloaddition yielding exclusively **14a** or **14b**, respectively. Both of these

(5) (a) Spino, C. *Synlett* **2006**, 23−32. (b) Spino, C.; Hill, B.; Dubé, P.; Gringras, S. *Can. J. Chem.* **2003**, *81*, 81−108.

(6) For reviews on the synthetic application of the Diels−Alder cycloaddition, see: (a) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1990. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. For reviews on an intramolecular Diels−Alder cycloaddition, see: (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807. (d) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 364−474. For reviews on a hetero-Diels−Alder cycloaddition, see: (e) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1−120. (f) Boger, D. L.; Weinreb, S. N. In *Hetero-Diels−Alder Methodology*; Wassermann, H., Ed.; Acedemic Press: New York, 1987; Vol. 47. (g) Weinreb, S. N.; Staib, R. S. *Tetrahedron* **1982**, *38*, 3087−3128.

(7) Dion, A.; Dubé, P.; Spino, C. *Org. Lett.* **2005**, *7*, 5601−5604.

(8) For selected discussions of thiocarbonyl compounds as dienophiles, see: (a) Vedejs, E.; Galante, R. J.; Goekjian, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 3613−3622. (b) Rohr, U.; Schatz, J.; Sauer, J. *Eur. J. Org. Chem.* **1998**, *2875*, 5−2883.

(9) (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.

(10) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791−1799.

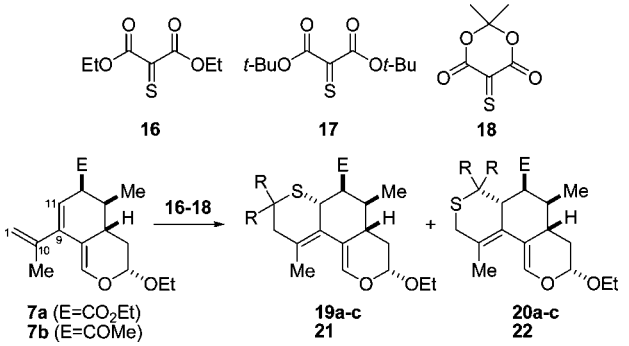
structures were confirmed by single-crystal X-ray diffraction analysis.[11] We believe the stereoselectivity of this unique cycloaddition comes from conformational constraints. The endo orientation of the internal carbonyl of the dienophile imparts quite a bit of conformational strain to the system.

Unmasking of α,β-unsaturated aldehydes **15a**,**b**[12] was followed by a second, endo-selective [4+2]-cycloaddition involving ethylvinyl ether (EVE) and $Yb(fod)_3$ as the catalyst (Scheme 3).[13] Cycloadducts **6a** or **6b** can be isolated as single diastereomers if the reaction is run at 25 °C.[11] However, and gratifyingly, both compounds underwent the desired decarboxylation reaction when the reaction was run in refluxing benzene to give directly **7a**,**b** from **15a**,**b** (cf. Scheme 1).

The result of the next Diels−Alder cycloaddition would decide the fate of our strategy. We were looking for a carbon−heteroatom dienophile because the resulting cycloadduct would then contain two cleavable C−Z bonds (cf. Scheme 2). It seemed to us that a thiocarbonyl compound was a good choice because of the ease with which carbon−sulfur bonds can be manipulated (e.g., desulfurization, elimination, or Pummerer rearrangement).[14] We also considered carbonyl compounds as dienophiles and tested several without success (none would undergo the cycloaddition). In general, thiocarbonyls are more reactive than the corresponding carbonyls and react with 1,3-dienes at exceptionally low temperatures.[6g] This increased reactivity originates from their weaker π-bond and lower LUMO orbital.[15,16]

We prepared three thiones according to the methodology developed by Albelman (Table 1).[16] Treatment of bromomalonates with sulfur powder and triethylamine led, via a simple addition−elimination sequence, to the corresponding thiones **16**−**18** which reacted in situ with dienes. Table 1 summarizes the results of their cycloaddition with 1,3-diene **7a**.

Table 1. Cycloadditions between **7a**,**b** and **16**−**18**

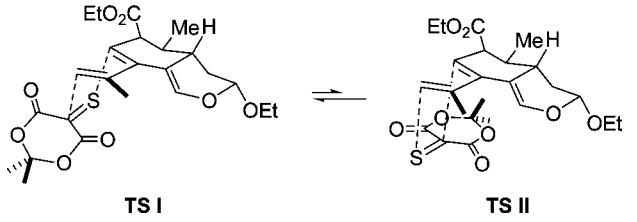


1,3-diene	thione	T (°C)	yield (%)	ratio
	16[a]	rt	81	1:2 (**19a**/**20a**)[b]
7a	**17**[a]	60	92	2:1 (**19b**/**20b**)[c]
	18[a]	82	80	14:1 (**19c**/**20c**)[b]
7b	**18**[d]	−10	63	30:1 (**21**[b]/**22**)

[a] Generated by Albelman's methodology.[16] [b] See ref 11. [c] Structure of **20b** was confirmed by desulfurization to the vinylic *gem*-dimethyl compound. [d] Generated by Capozzi's methodology.[17]

Diethyl thiomalonate **16** reacted at room temperature to afford a 1:2 mixture of cycloadducts **19a** and **20a**. Both compounds arise from an attack of the dienophile on the less-hindered α-face of the diene. The observed regioselectivity is not easily explained by FMO theory. In any case, we believed that steric effects could reverse this selectivity. We thus investigated bulkier thiones. As hoped, substitution of both ethyl esters for *tert*-butyl esters on the thione (**17**) led to the preferred formation of the desired regioisomer in a 2:1 ratio. Ultimately, thione **18**, derived from Meldrum's acid, led to a 14:1 ratio of the cycloadducts **19c** and **20c**. Although the fixed (*O*)-*E* conformation of the esters in **18** probably affects the electronics of the thione, steric effects are likely prominent in controlling the regiochemistry of this cycloaddition. The rigid structure of **18** may increase its steric demand, which would destabilize transition state **TS II** more effectively (Scheme 4).

Scheme 4. Transition States for the HDAC of **7a** and **18**



We repeated the cycloaddition of **18** with **7b** with similar results. In addition, using the method of Capozzi and coworkers to generate **18**, we were able to perform the cycloaddition at −10 °C to yield **21** and **22** in a 30:1 ratio.[17] The structure of **21** was confirmed by single-crystal X-ray diffraction analysis.[11]

Concomitant methanolysis and decarboxylation of **21** were accomplished using a catalytic amount of $Ni(acac)_2$ (Scheme 5).[18] Desulfurization to **23** and complete reduction of the ester and ketone to the corresponding diol followed by a double oxidation led to aldehyde **24**.[19] The dienophile necessary for the final intramolecular cycloaddition was

(11) Details of crystal structure analyses are provided as Supporting Information. CCDC 600917 (**14a**), CCDC 600922 (**14b**), CCDC 600615 (**6a**), CCDC 600923 (**6b**), CCDC 600918 (**19a**), CCDC 600926 (**20a**), CCDC 600919 (**19c**), CCDC 600925 (**20c**), and CCDC 600924 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575−578.

(13) Danishefsky, S. J.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721−724.

(14) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401−2432 and references therein.

(15) (a) Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556−1562. (b) Vedejs, E.; Perry, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 6999−7001.

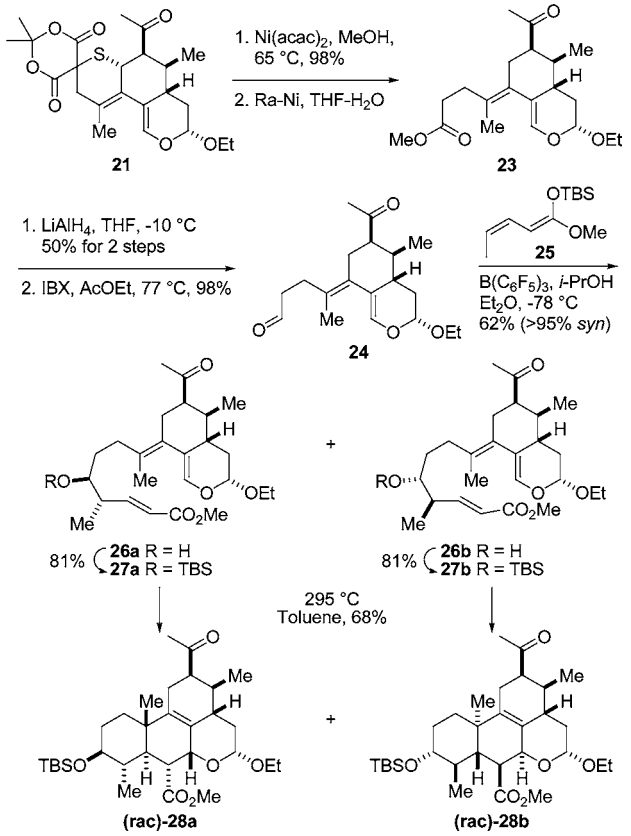
(16) Albelman, M. M. *Tetrahedron Lett.* **1991**, *32*, 7389−7392.

(17) Capozzi, G.; Menichetti, S.; Nativi, C.; Rosi, A.; Valle, G. *Tetrahedron* **1992**, *48*, 9023−9032.

(18) All acidic conditions tried gave decomposition products. $Ni(acac)_2$ gave the best results.

(19) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003.

Scheme 5. Synthesis of Tetracyclic Intermediates **28a**,**b**



introduced by performing a syn- and γ-selective vinylogous Mukaiyama aldol reaction with ketene acetal **25**.[20] Because aldehyde **24** is racemic and **25** is achiral at this stage, both syn diastereomers **26a** and **26b** were formed in 1:1 ratio as an inseparable mixture. An asymmetric version of this vinylogous aldol exists[21] and will be used with a nonracemic aldehyde **24** that is being prepared using chemistry previously published.[22] The free secondary alcohols in **26a**,**b** were then protected as their silyl ethers. Heating the 1:1 mixture of **27a** and **27b** to 295 °C for 2 h resulted in the exclusive formation of two separable tetracyclic compounds **28a**,**b** in 68% yield.

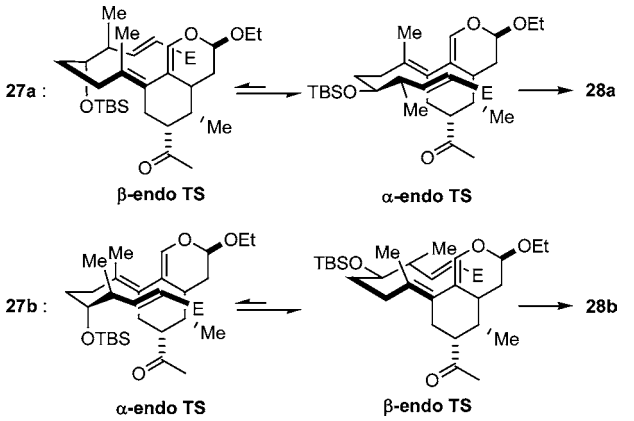
(20) Hassfeld, J.; Christmann, M.; Kalesse, M. *Org. Lett.* **2001**, *3*, 3561−3564.

(21) Schlessinger, R. H.; Li, Y.-J.; Von Langen, D. J. *J. Org. Chem.* **1996**, *61*, 3226−3227.

(22) Spino, C.; Fréchette, S. *Tetrahedron Lett.* **2000**, *41*, 8033−8036.

The relative stereochemistries in **28a** and **28b** were unambiguously determined by 2D-NMR analysis. This result means that cycloaddition of **27a** occurred exclusively via an α-endo TS to yield tetracyclic compound **28a**, whereas **27b** also underwent a stereoselective cycloaddition to give **28b** via a β-endo TS (Scheme 6). These two TSs are lower

Scheme 6. Proposed Transition States for the IMDAC of **27a**,**b**



in energy because of the pseudoequatorial orientation of the methyl and silyloxy groups. Tetracycle **28a** contains sufficient synthetic levers around its carbon skeleton to be used in the completion of the synthesis of several natural quassinoids.

In conclusion, the convergent and stereoselective synthesis of tetracycle **28a** was efficiently achieved in 18 steps from propargyl alcohol using a quadruple diene-transmissive Diels−Alder cycloaddition strategy. The dienophilic carbon chain was brought about in a very convergent manner using a regio- and stereoselective hetero-Diels−Alder reaction with Meldrum's acid-derived thione **18**. The syntheses of several natural quassinoids using this synthetic strategy are now underway 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 analyses data. This material is available free of charge via the Internet at http://pubs.acs.org.

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