ORGANIC LETTERS

2007
Vol. 9, No. 25
5163−5166

Vinigrol: A Compact, Diene-Transmissive Diels–Alder Strategy to the Tricyclic Core

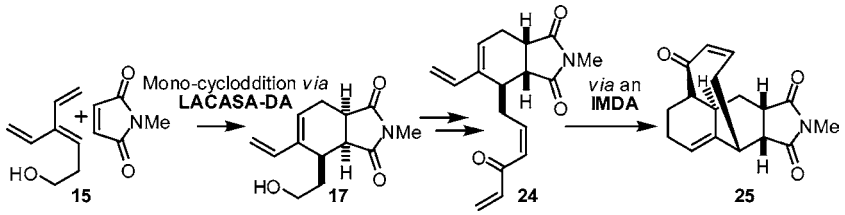
Michael Santos Souweha, Gary D. Enright,† and Alex G. Fallis*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

alexander.fallis@uottawa.ca

Received September 7, 2007

ABSTRACT



A short (six steps from 17), versatile route to the tricyclic core of Vinigrol is described. A Lewis acid catalyzed and self-assembled Diels–Alder (LACASA-DA) reaction from the homoallylic cross-conjugated trienol 15 with *N*-methylmaleimide afforded the monoadduct 17 with diastereo-, regio-, and chemoselective control. Oxidation and installation of an acetylene (Ohira's reagent) followed by further manipulations afforded trienone 24. The second intramolecular Diels–Alder (at 45 °C) reaction assembled the tricyclic skeleton 25 directly. The configuration of 25 was confirmed by X-ray analysis.

In the period since the isolation and structure elucidation of the novel trihydroxyditerpene Vinigrol, there has been a growing worldwide interest in this molecule (Figure 1).[1] This

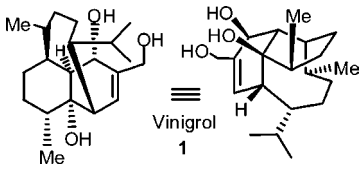


Figure 1. Structure of Vinigrol **1**.

is a consequence of its medicinal potential and unusual structure. Its medicinal attributes include its antihypertensive and platelet-inhibiting properties,[2] plus its promise as a powerful tumor necrosis factor antagonist capable of arresting the AIDS complex,[3a] the treatment of inflammation in combination with a cyclooxgenase 2 (COX-2) inhibitor,[3b] and as nerve stem cell proliferation promoter.[3c] The architecture is unique and presents several synthetic challenges for organic chemists. These include the *syn*-trihydroxy motif on the top face of the *cis*-decalin component and the hydrocarbon-substituted eight-membered bridge which joins the two individual cyclohexane rings.

Several synthetic approaches outlining different strategies to Vinigrol have been reported over the past dozen years. Briefly, these include the research groups of Hanna and Lallemand,[4] Kito and Matsuda,[5] Mehta,[6] Paquette,[7] and

† Current address: Steacie Institute for Molecular Sciences, NRC, Ottawa, Ontario, K1A 0R6, Canada. E-mail: Gary.Enright@nrc-cnrc.gc.ca, for X-ray enquiries.

(1) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292.

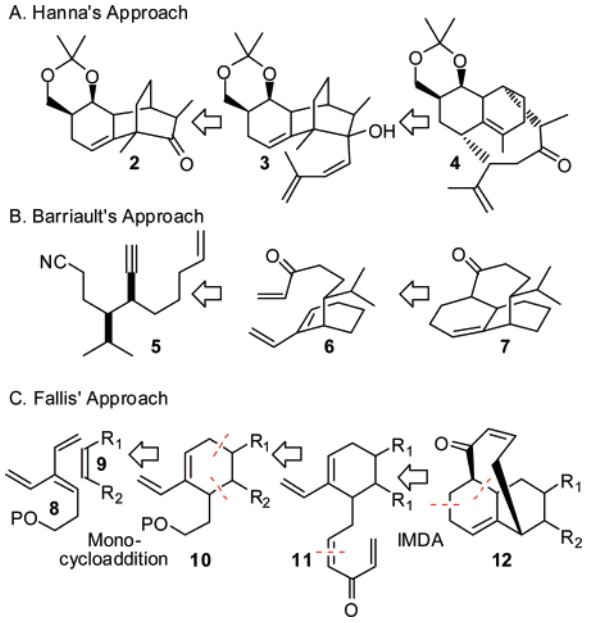
(2) (a) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 25−30. (b) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31−35.

(3) (a) Norris, D. B.; Depledge, P.; Jackson, A. P. PCT Int. Appl. WO 91 07 953; *Chem. Abstr.* **1991**, *115*, 64776h. (b) Keane, J. T. PCT Int. Appl. WO 2001000229. (c) Onodera, H.; Ichimura, M.; Sakurada, K.; Kawabata, A.; Ota, T. PCT Int. Appl. WO 2006077954.

10.1021/ol702202b CCC: $37.00
Published on Web 11/14/2007

Barriault.[8] These reports encompass a diverse collection of strategies from oxy-Cope rearrangements, samarium diiodide mediated cyclizations, ring expansions, transannular cyclization protocols, and installation of additional functionality to constrain a synthetic intermediate and facilitate the desired transformation. Ring closing metathesis sequences from a *cis*-decalin core to close the cyclooctene bridge appeared attractive but failed.[7a,8a] Scheme 1 briefly summarizes the

Scheme 1. Current Approaches Toward the Core Structure of Vinigrol



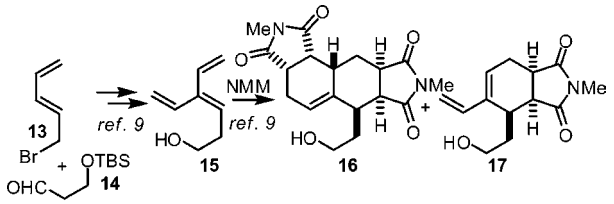
two reported routes to the Vinigrol core via an oxy-Cope rearrangement, and in parallel with our own research, our colleague Louis Barriault has also utilized an IMDA construction step.[8c] The challenges uncovered by others and ourselves implied that a sequential intramolecular cycloaddition strategy in which initially an in situ tether-fixed tether combination might minimize some of the previous complications that Nature has imposed.

Our approach was predicated on our recent pentadienyl indium chemistry[9] in which a Lewis acid catalyzed and self-assembled Diels–Alder cycloaddition (LACASA-DA) occurred via a temporary magnesium template that controls the initial in situ cyclization.[10] Some recent synthetic examples also utilize this Diels–Alder strategy (LACASA-DA) as an important step for natural product construction.[11]

Our experience with the synthesis of the eight-membered ring in taxoids revealed that their assembly is facilitated by incorporation of an *endo-cis* double bond plus suitably juxtaposed oxygen functionality for cross-ring Lewis acid complexation.[12] These features have been incorporated into our design to facilitate the cyclization and provide additional functionality for future manipulation. Consequently, the retrosynthetic sequence from the adduct tricyclic **12**, to the enone **11**, to the initial adduct **10** suggested an attractive route to assemble the desired tricyclo[9.4.0]undecadienone skeleton.

Exposure of trieneol **15** to methylmagnesium bromide and *n*-pentanol afforded the adduct **17** as the major product (Scheme 2). Oxidation of the primary alcohol with PCC

Scheme 2. Synthesis of Mono-Cycloadduct **17** from an in situ Tether Cycloaddition Reaction



proceeded smoothly, and condensation of the resulting aldehyde **18** with the dimethyl 1-diazo-2-oxopropylphosphonate (Ohira reagent, **26**)[13] afforded the acetylene **19**[14] directly in 78% yield (Scheme 3). This requires 24 h at rt and an excess of cesium carbonate. Under these conditions, the original stereochemistry is inverted to afford the *exo*-isomer as illustrated in Figure 2.[15] This was not anticipated,

(4) (a) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prangé, T. *J. Org. Chem.* **1993**, *58*, 2349–2350. (b) Devaux, J.-F.; Fraisse, P.; Hanna, I.; Lallemand, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 9471–9474. (c) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1997**, *62*, 5062–5068. (d) Gentric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, *5*, 1139–1142.

(5) (a) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057–1060. (b) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 14369–14380.

(6) Mehta, G.; Subba Reddy, K. *Synlett* **1996**, 625–627.

(7) (a) Paquette, L. A.; Efremov, I.; Liu, Z. *J. Org. Chem.* **2005**, *70*, 505–509. (b) Paquette, L. A.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 510–513. (c) Paquette, L. A.; Liu, Z.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 514–518. (d) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096–6107.

(8) (a) Barriault, L.; Morency, L. *Tetrahedron Lett.* **2004**, *45*, 6105–6108. (b) Morency, L.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 8841–8853. (c) Grisé, C. M.; Tessier, G.; Barriault, L. *Org. Lett.* **2007**, *9*, 1545–1548. (d) Review: Tessier, G.; Barriault, L. *Org. Prep. Proc. Int.* **2007**, *39*, 311–353.

(9) Souweha, M. S.; Arab, A.; ApSimon, M.; Fallis, A. G. *Org. Lett.* **2007**, *9*, 615–618.

(10) For key references on Lewis acid catalyzed and self-assembled Diels-Alder reactions (LACASA-DA), see: (a) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937–3940. (b) Ward, D. E.; Souweha, M. S. *Org. Lett.* **2005**, *7*, 3533–3536. (c) Souweha, M. S. Regioselective and Stereoselective Diels–Alder Reactions via a One or Two Metal Center Template. Ph.D. Dissertation, The University of Saskatchewan, Saskatoon, SK, September 2006. (d) For a templated copper dimerization, see: Heuft, M. A.; Fallis, A. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4520–4523.

(11) (a) Nicolaou, K. C.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3256–3260. (b) Zografos, A. L.; Yiotakis, A.; Georgiadis, D. *Org. Lett.* **2005**, *7*, 4515–4518. (c) Rath, J.-P.; Kinast, S.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3089–3092. (d) Barriault, L.; Ang, P. J. A.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317–1319.

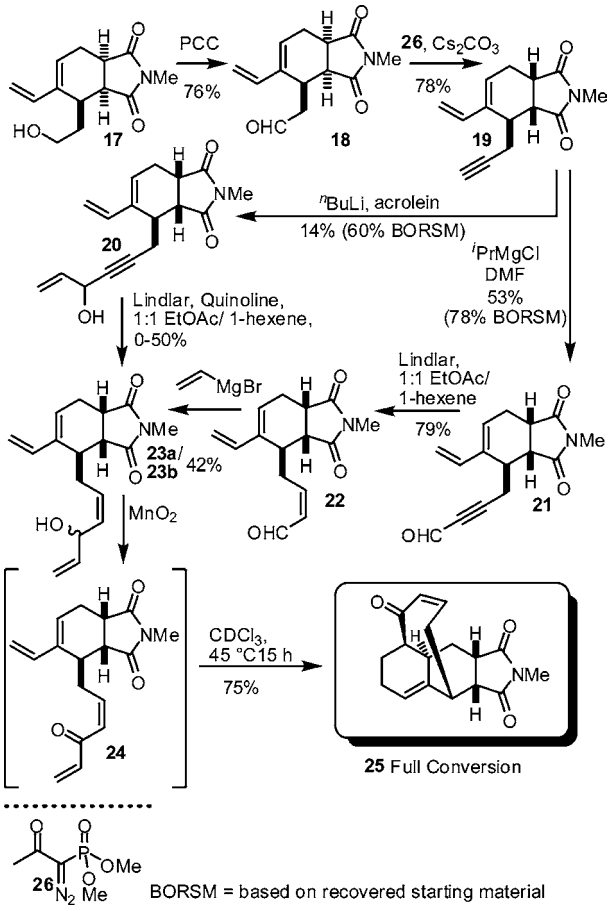
(12) (a) Smil, D. A.; Laurent, A.; Villava-Serin, N. P.; Forgione, P.; Wilson, P. D.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 215–226. (b) Forgione, P.; Wilson, P. D.; Yapp, G. P. A.; Fallis, A. G. *Synthesis* **2000**, 921–924.

(13) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564.

(14) CCDC 659676 contains 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.

(15) Kwart, H.; Burchuk, I. *J. Am. Chem. Soc.* **1952**, *74*, 3094–3097.

Scheme 3. Conversion of Adduct **17** to Adduct **25**



but this serendipitous event may be a bonus for a total synthesis due the new orientation of the heterocyclic ring.

Treatment of the alkyne with ^{n}BuLi and condensation with acrolein provided a small sample of the allylic alcohol **20**. Different protocols were examined to manipulate the triple bond and introduce the *cis*-alkene to facilitate the ultimate cycloaddition. There are numerous studies in the literature to modify the traditional Lindlar catalyst to fine tune its reactivity for delicate reactions.[16] The selective reduction of **20** is a demanding case due to the presence of three olefins, one of which is monosubstituted allylic. The use of Lindlar catalyst with quinoline in a mixed solvent of ethyl acetate/ 1-hexene (1:1) gave an irreproducible low yield of a mixture of reduced products.[17] The sensitivity of this substrate dictated we develop a better protocol.

Consequently, generation of the alkynyl anion with isopropylmagnesium chloride followed by condensation with dimethylformamide and hydrolysis afforded the alkynylaldehyde **21** in 78% yield based on recovered starting material. Extensive experimentation revealed the following conditions gave consistent results. Reduction of the alkynal with Lindlar catalyst, in the absence of quinoline, in a solvent comprising a 1:1 ratio of ethyl acetate and 1-hexene afforded the requisite unsaturated aldehyde **22** (*cis*/*trans* 6:1).[18] Addition of vinylmagnesium bromide afforded a 1:1 mixture of epimeric alcohols. Oxidation with manganese dioxide gave the desired enone **24**, which was used directly for the final step.

The cyclization of the Diels−Alder precursor was particularly facile, and no added catalyst was required. Formation of the tricyclic adduct can be observed in the ^{1}H NMR spectrum of the enone **24**. In addition, this cycloaddition occurred spontaneously over 2 days at room temperature. On a preparative scale, heating the **24** in deuterochloroform at 45 °C for 15 h provided quantitative conversion to the tricyclic core of Vinigrol (**25**). Analysis of its X-ray structure in Figure 3[19] confirms the orientation of the substituents,

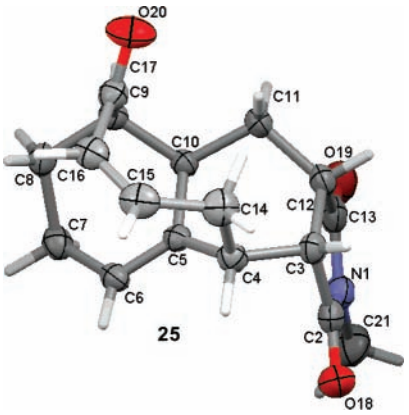


Figure 3. X-ray structure of tricyclic Vinigrol core **25**.

the stereochemistry, the relative disposition of the three rings, and the absence of any rearranged structure.[20]

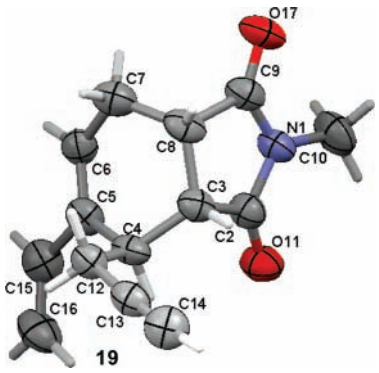


Figure 2. X-ray structure of bicyclic alkyne **19**.

(16) Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89−92.

(17) Under several Lindlar-type conditions, the reduction of **20** gave over reduced products presumably due to the reactivity of the bis-allylic alcohol.

(18) The minor product was not assigned unambiguously. Presumably formed from isomerization of *cis*-**22** (i.e., not reduction of **21**) as the *trans*/*cis* ratio increases with time in $CDCl_3$ and under the reaction conditions.

(19) CCDC 659678 contains 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.

(20) The skeleton of Vinigrol has been shown to rearrange under acidic conditions; see: Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prange, T. *J. Chem. Res., Synop.* **1996**, 32−33.

In summary, the application of an initial mono-Lewis acid catalyzed and self-assembled Diels−Alder cycloaddition (LACASA-DA) reaction, functional group manipulation, and a subsequent intramolecular [4 + 2] cycloaddition to incorporate the cyclooctane bridge provided a direct route to the tricyclic core of Vinigrol in a very efficient manner (six steps from **17**). This sequential cycloaddition strategy expands the potential and indicates the versatility of our triene ([3]dendralene) chemistry for a variety of synthetic objectives including more complex natural product skeletons.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support of this research.

Supporting Information Available: Experimental details and spectral characterization for these compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702202B