

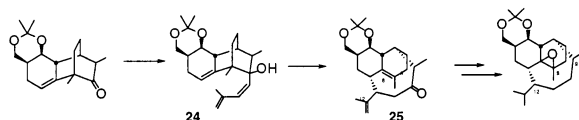
Synthesis of the Complete Carbocyclic  
Skeleton of VinigrolLionel Gentric,<sup>†</sup> Issam Hanna,<sup>\*,†</sup> and Louis Ricard<sup>‡</sup>

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## ABSTRACT



An efficient entry to the fully elaborated skeleton of vinigrol is described. The installation of the desired stereochemistry at C(12) and the construction of the eight-membered ring were achieved in one operation by a remarkably facile anionic oxy-Cope rearrangement of *Z*-isopropenyl isomer 24.

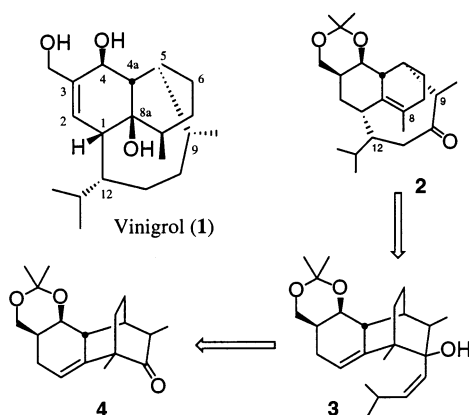
Vinigrol (**1**) is a diterpenoid isolated in 1987 from a culture of the fungal strain identified as *Virgaria nigra*.<sup>1</sup> Very early on, it was demonstrated that this natural product decreased arterial blood pressure in rats in a dose-dependent manner and inhibited platelet activating factor and epinephrine induced platelet aggregation.<sup>2</sup> In addition, it was found that **1** is a powerful tumor necrosis factor (TNF) antagonist. Therefore, vinigrol may be used for the treatment of endotoxic shock inflammation, infections, and cachexia and to arrest progression from AIDS-related complex to AIDS.<sup>3</sup> Structurally, vinigrol possesses a unique tricyclic skeleton **2**, involving a bridged eight-membered ring. The unusual structure of this natural product combined with its interesting biological activities provide a challenging synthetic target. However, despite the efforts of many groups,<sup>4</sup> a complete total synthesis of **1** has yet to be reported. As for cyclo-octanoid substances, the most critical issue in the synthesis

of vinigrol is the construction of the eight-membered ring. Our strategy is based on the recognition that the oxygenated tricyclic skeleton **2** of vinigrol can be quickly elaborated via an anionic oxy-Cope rearrangement<sup>5</sup> of a tricyclic vinyl carbinol such as **3**, which could arise from stereoselective alkylation of enone **4** (Scheme 1). Previous results from our laboratory established the feasibility of this approach and described the first successful entry into the functionalized decahydro-1,5-butanonaphthalene ring system of this natural product in a very concise manner.<sup>6</sup> However, the previously described model was not adequately functionalized for the expeditious completion of the synthesis. In particular, the stereoselective introduction of the isopropyl group at C(12)<sup>7</sup> seemed to be a major problem. We now disclose an efficient

<sup>†</sup> Laboratoire de Synthèse Organique associé au CNRS.<sup>‡</sup> Laboratoire “Hétéroéléments et Coordination” associé au CNRS.(1) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292–5293.(2) (a) Ando, T.; Tsurumi, Y.; Ohata, N.; Ushida, I.; Hoshida, 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.; Jakson, A. P. PCT Int. Appl. WO 91 07,953; *Chem. Abstr.* **1991**, *115*, 64776. (b) Nakajima, H.; Yamamoto, N.; Kaisi, T. Jpn. Kokai Tokyo Koho JP 07206668; *Chem. Abstr.* **1995**, *123*, 246812.(4) (a) Mehta, G.; Reddy, K. S. *Synlett* **1996**, 625–627. (b) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 14369–14380. (c) Efremov, I. V. Ph.D. Dissertation, The Ohio State University, 2001. (d) Goodman, S. N. Ph.D. Dissertation, Harvard University, 2000.(5) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766. For reviews on stereocontrolled construction of complex cyclic ketones via Oxy-Cope rearrangements see: Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609–626. Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971–14020.(6) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prangé, T. *J. Org. Chem.* **1993**, *58*, 2349–2350. Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1997**, *62*, 5062–5068.

(7) The numbering used in this paper refers to the corresponding centers of vinigrol.

Scheme 1



entry to the fully elaborated vinigrol carbon skeleton. In this study, methyl groups at C(8) and C(9) were introduced at the first stage and installation of the isopropyl at C(12) was planned before the oxy-Cope rearrangement as outlined in Scheme 1. To this end the tricyclic ketone **4**, bearing the methyl groups and conveniently positioned oxygen functionalities, was first elaborated.

The synthesis began with the readily available trimethylsilyl enol ether **5**<sup>8</sup> (Scheme 2). Heating this diene in the presence of 1,4-benzoquinone in THF gave **7** in quantitative yield. Treatment of **7** with a catalytic amount of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in THF at  $-70^\circ\text{C}$  cleanly led to the mixed trimethylsilyl ketal **8**. This alcohol was submitted to the Mitsunobu inversion,<sup>13</sup> using 4-nitrobenzoic acid,<sup>14</sup> followed by cleavage of the resulting ester under mild conditions ( $\text{K}_2\text{CO}_3$ ,  $\text{MeOH} - \text{Et}_2\text{O}$ ) to give **9**. It is worthy of note that the first chromatographic purification only occurred at this stage. The overall yield of this five-step sequence, conveniently executed on a 20-g scale, was 65–70%.

Next, the hydroxymethyl group at C(3) was stereoselectively introduced, using the Stork procedure.<sup>15</sup> Thus, bromomethyldimethylsilyl ether **10**, prepared by silylation of **9** ( $\text{BrCH}_2\text{SiMe}_2\text{Cl}$ , DMAP,  $\text{Et}_3\text{N}$ ), was subjected to standard high-dilution, radical-generating conditions followed by Tamao oxidation<sup>16</sup> ( $\text{H}_2\text{O}_2$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{THF} - \text{MeOH}$ ) to furnish diol **11**.

(8) Diene **5** was prepared from the commercially available 2,6-dimethylcyclohexanone by oxidation with NBS in refluxing  $\text{CCl}_4$  (4 h) in the presence of a catalytic amount of AIBN (90%)<sup>9</sup> followed by silylation of the resulting 2,6-dimethylcyclohex-2-enone.<sup>10</sup>

(9) Kende, A. S.; Fludzinski, P. H.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551–3562.

(10) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051–1056.

(11) For similar transformations see: (a) Hung, S. C.; Liao, C. C. *Tetrahedron Lett.* **1991**, *32*, 4011–4014. Hung, S. C.; Liao, C. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1457–1458. (b) Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1994**, *116*, 11213–11228.

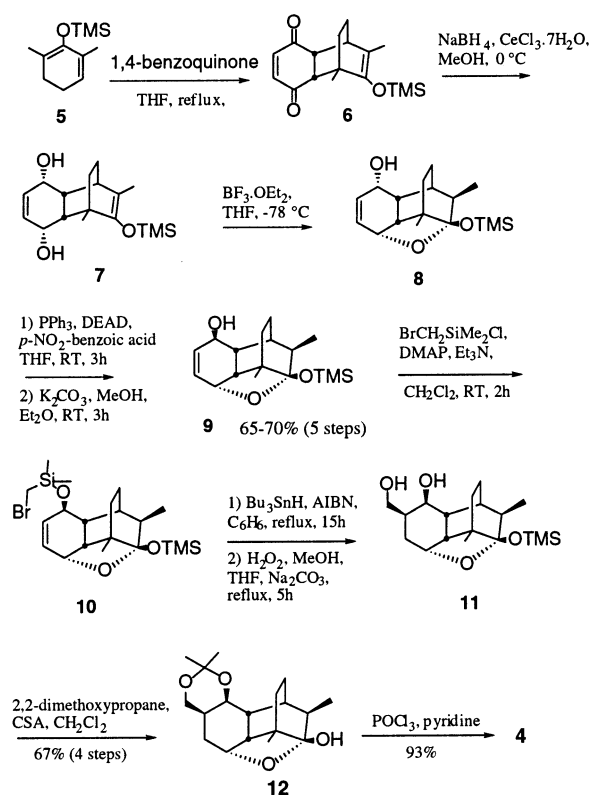
(12) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(13) Mitsunobu, O. *Synthesis* **1981**, 1–28. Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.

(14) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234–236.

(15) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500–501.

Scheme 2



Treatment of **11** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid resulted in the formation of the acetonide protecting group concomitant with hydrolysis of the mixed TMS ketal affording **12** in 67% overall yield for the four-step sequence. Dehydration of **12** with phosphorus oxychloride in pyridine led to the key tricyclic ketone **4** in 93% yield.

Exposure of **4** to 3-methylbutynylmagnesium bromide<sup>17</sup> in THF gave rise to a 4.2:1 mixture of *exo*- and *endo*-propargyl alcohols **13** and **14** (94%) which were readily separated by flash chromatography. In contrast to previous observations in the model study,<sup>6</sup> the presence of the *exo*-methyl group at C(9) in **4**<sup>20</sup> promoted the addition of the Grignard reagent from the sterically less hindered *endo* face. Since the oxy-Cope rearrangement proceeds via a chairlike transition state, introduction of an isopropyl at C(12) with the desired configuration requires a *Z*-geometry of the double bond in the allylic alcohol precursor **15**. This compound was

(16) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983–990. Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96–105.

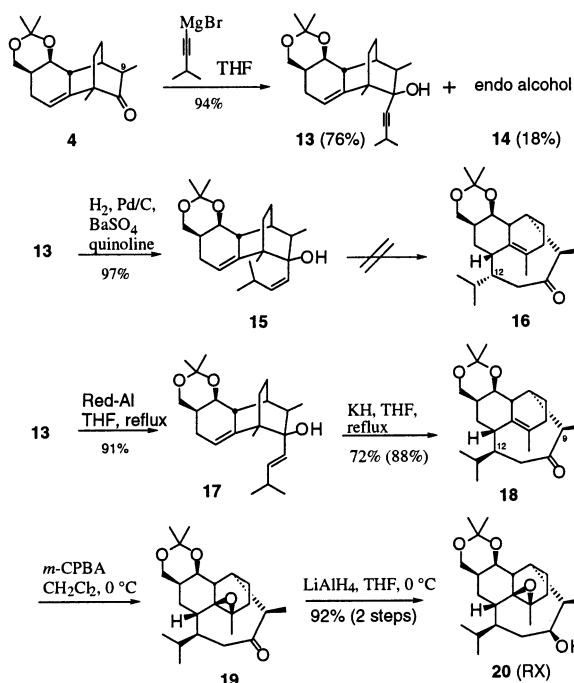
(17) This Grignard reagent was prepared by the action of ethylmagnesium bromide on isopropylacetylene, which was obtained from 2-methylbut-3-yn-1-ol in two steps: bromination (47% aq HBr, CuBr,  $\text{NH}_4\text{Br}$ , Cu)<sup>18</sup> followed by reduction of the resulting bromoallene with  $\text{LiAlH}_4$  in DME.<sup>19</sup>

(18) Landor, S. R.; Patel, A. N.; Whiter, P. F.; Greaves, P. M. *J. Chem. Soc. C* **1966**, 1223–1226.

(19) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309–3326.

(20) The *exo* configuration of the methyl group at C(9) was confirmed by X-ray crystallographic analysis of an analogue compound.<sup>21</sup>

Scheme 3

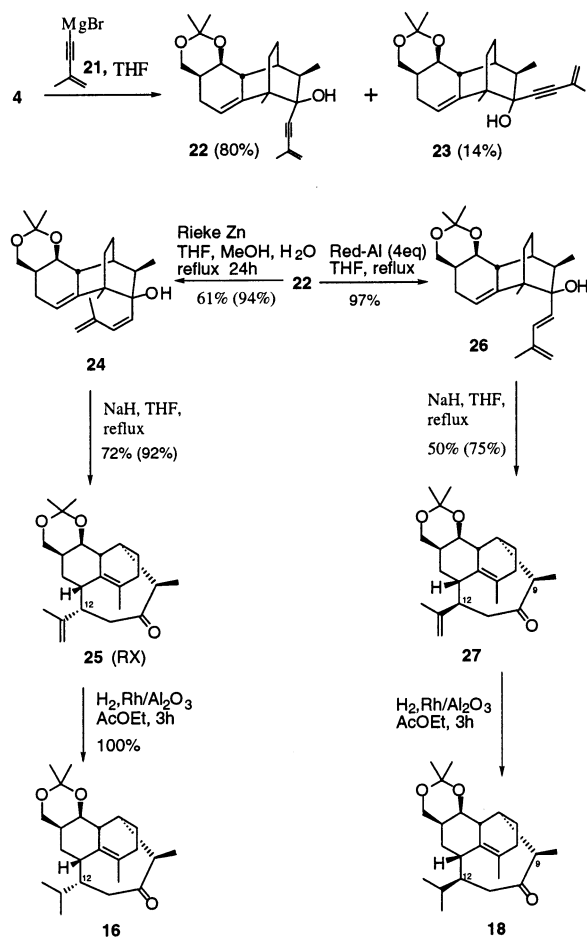


easily obtained by semihydrogenation of **14** ( $\text{H}_2$ ,  $\text{BaSO}_4$ , quinoline) (Scheme 3). However, all attempts of oxy-Cope rearrangement on **15** under a variety of anionic (KH or KHMDS in refluxing THF or toluene, with 18-Cr-6) or thermolytic (refluxing Decalin) conditions failed. The starting alcohol was either recovered unchanged or decomposed, depending upon the experimental conditions. Obviously, there is considerable steric crowding between the olefinic moiety and the isopropyl group when the side chain of **15** is forced to reach the transition state, which impedes any concerted rearrangement. In contrast, when the *E*-isomer **17** was subjected to potassium hydride in refluxing THF, compound **18** was isolated in 78% yield. This structure was assigned on the basis of spectroscopic data and the configuration of alkyl groups was confirmed later by X-ray crystallographic analysis of epoxyalcohol **20**. Both alkyl groups at C(9) and C(12) have the opposite stereochemistry to that of vinigrol (Scheme 3). While epimerization at C(9) could be achieved under basic conditions, the inversion of the configuration of isopropyl at C(12) seemed to be a major hurdle again.

Many approaches were surveyed to solve this problem without success.<sup>21</sup> After considerable experimentation, the solution came from an unexpected observation. We were pleased to discover that when the isopropyl group in **15** was replaced by an isopropenyl (compound **24**, Scheme 4), the oxy-Cope rearrangement took place affording the skeleton of vinigrol with the correct relative configuration at C(12). Alcohol **24** was prepared from ketone **4** as indicated in Scheme 4. Treatment of **4** with an excess of Grignard reagent **21**<sup>22</sup> gave a separable mixture of exo and endo alcohols **22**

(21) Details will be reported later in the full account of this work.

Scheme 4



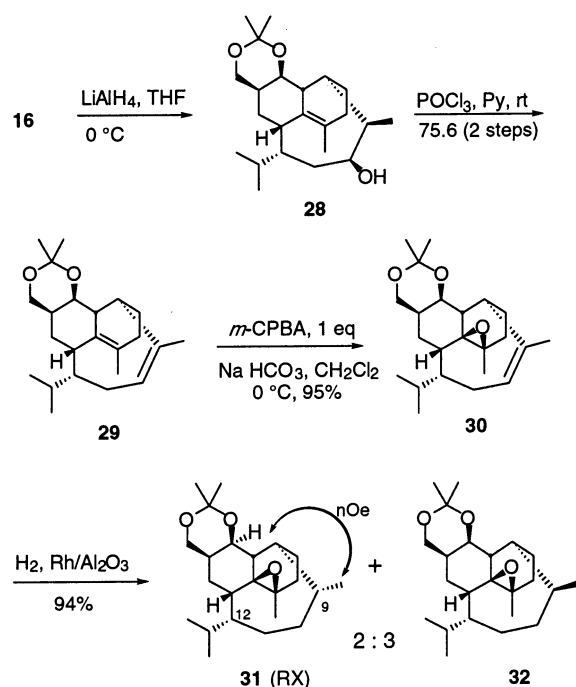
and **23** in 80% and 14% yields, respectively. Reduction of **22** with Rieke zinc<sup>23</sup> cleanly provided diene **24** in good yield (61%, 94% based on recovered enyne).<sup>24</sup> Exposure of **24** to KH in refluxing THF for 1 h led to the rearrangement product **25** in 50% along with the starting material (20%). The structure of **25** was deduced from the spectroscopic data, and the relative configuration of isopropenyl at C(12) was confirmed by X-ray crystallographic analysis. Catalytic hydrogenation of **25** in the presence of rhodium on alumina gave **16** in quantitative yield. After a brief survey of reaction conditions, we found that simply heating **24** and NaH (instead of KH) in THF for 18 h cleanly produced **25** in 72% yield (92% based on recovered starting material) with high reproducibility.<sup>25</sup> This observed rate acceleration is probably the result of stabilization of the transition state of the anionic oxy-Cope rearrangement by an additional unsaturation on the terminal position.<sup>26</sup> Under the same conditions, *E*-isomer **26** underwent the same rearrangement affording **27** in 50%

(22) Grignard reagent **22** was prepared from 2-methyl-1-en-3-yne (Brandsma, L. In *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 1988; p 203) and ethylmagnesium bromide in THF-ether at room temperature.

(23) Rieke, R. D. *Aldrichim. Acta* **2000**, 33, 52–60. Chou, W. N.; Clark, D. L.; White, J. B. *Tetrahedron Lett.* **1991**, 32, 299–302.

(24) Semihydrogenation of the triple bond with Lindlar's catalyst led to a mixture of products from which the desired diene **23** was isolated in 30–40% yield.

Scheme 5



(75%) yield. Subsequent catalytic hydrogenation of **27** provided **18**, previously obtained from **17**.

With the required relative configuration of the isopropyl at C(12) in hand, we turned to the next phase of the

(25) In this reaction NaH (80% dispersion in mineral oil) was used without washing, and the solvent was not degassed. In contrast, exposure of **23** to oil-free KH in carefully degassed THF at reflux for more than 3 h led to a mixture of products from which **24** was isolated in modest yield.<sup>21</sup>

synthesis: removal the carbonyl group at C(10) and inversion of C(9) methyl stereochemistry. To this end ketone **16** was reduced with  $\text{LiAlH}_4$  and the resulting alcohol **28** was dehydrated with  $\text{POCl}_3$  to afford diene **29** (Scheme 5). Treatment of **29** with 1 equiv of *m*-CPBA at 0 °C selectively affected the tetrasubstituted double bond leading to epoxide **30** in 95% yield.<sup>27</sup> The remaining double bond was then hydrogenated in the presence of rhodium on alumina to give a 2:3 mixture of **31** and **32** in 94% yield. The relative configuration of the methyl group at C(9) in **32**, which was established by NOESY and confirmed by X-ray crystallographic analysis, was found to be the same compared with that of vinigrol.

In summary, this work describes an efficient synthesis of the complete carbocyclic skeleton of vinigrol. Our finding of the remarkable rate acceleration of the oxy-Cope rearrangement of *Z*-isopropenyl isomer provided a neat solution to the major hurdle in this synthesis. As a result, construction of the eight-membered ring and introduction of isopropenyl at C(12) with the correct stereochemistry were achieved in one operation. With compound **31**, we have in hand an advanced precursor that may hold the key to a successful total synthesis of vinigrol.

**Supporting Information Available:** Experimental procedure and characterization data for compounds **4**–**32**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(26) To our knowledge, only one example of such an effect has hitherto been reported. See: Paquette, L. A.; DeRussy, D. T.; Rogers, R. D. *Tetrahedron* **1988**, *44*, 3139–3148.

(27) Initial attempts to carry out the epoxidation of **29** failed: the resulting epoxide rapidly underwent an intramolecular ring opening by the hydroxyl group producing the corresponding cyclic ether.