

Formal Total Synthesis of (\pm)- α - and β -Cedrene by Preparation of Cedrone. Construction of the Tricyclic Carbon Skeleton by the Use of a Highly Efficient Intramolecular Khand Annulation

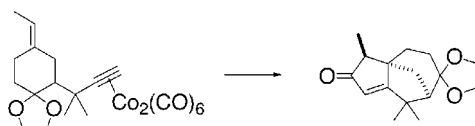
William J. Kerr,* Mark McLaughlin, Angus J. Morrison, and Peter L. Pauson

Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1XL, U.K.

w.kerr@strath.ac.uk

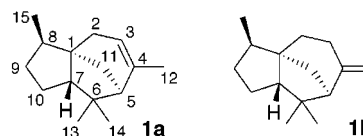
Received May 2, 2001

ABSTRACT



The cedrene carbon skeleton was rapidly assembled from a simple monocyclic precursor by the strategic use of a high yielding intramolecular Khand cyclization reaction. Further synthetic manipulations provided a concise formal total synthesis of α - and β -cedrene.

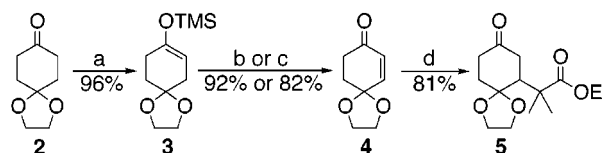
The naturally occurring tricyclic sesquiterpene α -cedrene **1a** can be isolated from *Juniperus cedrus* and *Juniperus thurifera*, alongside β -cedrene **1b** and a variety of closely related oxygenated terpenoid analogues.¹ Inspired by the intriguing [5.3.1.0^{1,5}] tricyclic structure, the cedrene family has generated great interest among the synthetic community² over the years since its characterization in 1953. As part of our ongoing endeavors to further develop the efficiency and applicability of the Khand cyclization reaction,³ we sought to strategically utilize this annulation process within routes toward α -cedrene **1a** and, in so doing, establish a direct and efficient pathway for the synthesis of this structurally



demanding tricyclic skeleton.

Our synthetic sequence begins (Scheme 1) with the introduction of α,β -unsaturation into the commercially available cyclohexanone monoethylene acetal **2**. To this

Scheme 1



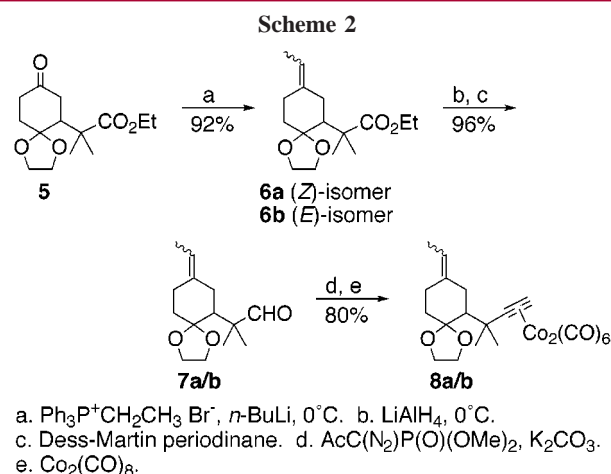
a. TMSOTf, Et₃N, -5°C. b. 1.05 eq. Pd(OAc)₂.
c. 5 mol% Pd(OAc)₂, 1.4 eq. diallyl carbonate, CH₃CN, 81°C.
d. 10 mol% Yb(OTf)₃·3H₂O, Me₂CC(OEt)OTMS.

(1) (a) Barrero, A. F.; del Moral, J. Q.; Lara, A. *Tetrahedron* **2000**, *56*, 3717 and references therein. (b) Stork, G.; Breslow, R. *J. Am. Chem. Soc.* **1953**, *75*, 3291. (c) Walter, P. *Ann. Chem.* **1841**, *39*, 247.

(2) For example see: (a) Stork, G.; Clark, F. H., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 1072. (b) Corey, E. J.; Girotra, N. N.; Mathew, C. T. *J. Am. Chem. Soc.* **1969**, *91*, 1557. (c) Crandall, T. G.; Lawton, R. G. *J. Am. Chem. Soc.* **1969**, *91*, 2127. (d) Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825. (e) Breitholle, E. G.; Fallis, A. G. *J. Org. Chem.* **1978**, *43*, 1964. (f) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688. (g) Rigby, J. H.; Kirova-Snover, M. *Tetrahedron Lett.* **1997**, *38*, 8153. (h) Lee, H.-Y.; Lee, S.; Kim, D.; Kim, B. K.; Bahn, J. S.; Kim, S. *Tetrahedron Lett.* **1998**, *39*, 7713.

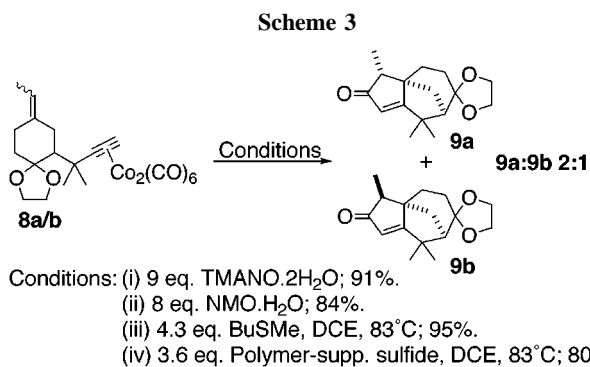
end, the enol ether **3** was easily prepared and then subjected to Saegusa oxidation conditions⁴ to afford enone **4**. Initially, a straightforward Saegusa reaction, using stoichiometric quantities of palladium(II) acetate, provided the enone **4** in 92% yield. However, based on the expense of the precious metal reagent, especially at such an early step in this synthesis program, the catalytic modification⁵ of this useful transformation was investigated. This more economical protocol was found to deliver **4** in a respectable 82% yield while requiring the use of only 5 mol % of palladium(II) acetate. Having secured a quantity of the desired enone, 1,4-addition of the trimethylsilyl enol ether of ethyl isobutyrate, catalyzed by ytterbium(III) triflate trihydrate,⁶ directly and efficiently afforded the ester **5** in a yield of 81%. Initial attempts to use titanium(IV) tetrachloride (the more traditional Lewis acid for this type of reaction) as a stoichiometric mediator of this Michael addition resulted in unwanted deprotection of the ketal, even at $-78\text{ }^{\circ}\text{C}$.

The next goal in our sequence was the ethyldienation of the ketone carbonyl of **5**. Indeed, it was projected that the stereochemical outcome of this process would impact upon the later stages of our synthetic pathway, with the (*E*)-isomer **6b** ultimately providing the requisite orientation of the C-15 methyl group of α -cedrene **1a**. Under standard Wittig reaction conditions a 92% yield of olefins **6a/b** was obtained, as an inseparable 2:1 mixture of geometric isomers. Consequently, **6a** and **6b** were utilized in combination in order to establish the planned synthetic route and with a view to identification of individual isomers at a later stage. In this respect, the remaining transformations toward the key cyclization precursors **8a/b** took place without difficulty (Scheme 2). Initial reduction of the ester functionality of **6a/b** with lithium aluminum hydride was followed by oxidation to aldehydes **7a/b** using the Dess–Martin periodinane⁷ in an overall yield of 96%. From the methods available for the conversion of aldehydes into terminal alkynes, we chose the Ohira–Bestmann reagent (dimethyl acetyldiazomethylphosphonate);⁸ previous experience in our laboratory had shown



this technique to be both practically simple and effective. Indeed, in this instance, this mild protocol furnished the requisite alkynes in 81% yield, and these were easily complexed with octacarbonyldicobalt to afford the stable cyclization precursors **8a/b** almost quantitatively. With these complexes in hand, we were now in a position to investigate the proposed Khand annulation for the assembly of the tricyclic carbon skeleton of α -cedrene.

A variety of methods for promoting the key intramolecular Khand cyclization of **8a/b** were examined (Scheme 3). These



included the use of two different amine *N*-oxides at room temperature,⁹ employment of a soluble alkyl methyl sulfide under more forcing conditions,¹⁰ and also the application of our recently developed solid-supported alkyl methyl sulfide.^{3d} It was found that, in all cases, the Khand cyclization took

(3) (a) Kennedy, A. R.; Kerr, W. J.; Lindsay, D. M.; Scott, J. S.; Watson, S. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4366. (b) Brown, D. S.; Campbell, E.; Kerr, W. J.; Lindsay, D. M.; Morrison, A. J.; Pike, K. G.; Watson, S. P. *Synlett* **2000**, 1573. (c) Ford, J. G.; Kerr, W. J.; Kirk, G. G.; Lindsay, D. M.; Middlemiss, D. *Synlett* **2000**, 1415. (d) Kerr, W. J.; Lindsay, D. M.; McLaughlin, M.; Pauson, P. L. *Chem. Commun.* **2000**, 1467. (e) Carbery, D. R.; Kerr, W. J.; Lindsay, D. M.; Scott, J. S.; Watson, S. P. *Tetrahedron Lett.* **2000**, *41*, 3235. (f) Kerr, W. J.; Lindsay, D. M.; Rankin, E. M.; Scott, J. S.; Watson, S. P. *Tetrahedron Lett.* **2000**, *41*, 3229. (g) Kerr, W. J.; Lindsay, D. M.; Watson, S. P. *Chem. Commun.* **1999**, 2551. (h) Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *Chem. Commun.* **1999**, 2171. (i) Clements, C. J.; Dumoulin, D.; Hamilton, D. R.; Hudecek, M.; Kerr, W. J.; Kiefer, M.; Moran, P. H.; Pauson, P. L. *J. Chem. Res., Synop.* **1998**, 636; *J. Chem. Res., Miniprint* **1998**, 2658. (j) Donkervoort, J. G.; Gordon, A. R.; Johnstone, C.; Kerr, W. J.; Lange, U. *Tetrahedron* **1996**, *52*, 7391. (k) Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Synlett* **1995**, 1085. (l) Gordon, A. R.; Johnstone, C.; Kerr, W. J. *Synlett* **1995**, 1083. (m) Hay, A. M.; Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Organometallics* **1995**, *14*, 4986. (n) Johnstone, C.; Kerr, W. J.; Lange, U. *J. Chem. Soc., Chem. Commun.* **1995**, 457.

(4) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(5) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5635. (b) Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971.
(6) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815.
(7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(8) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

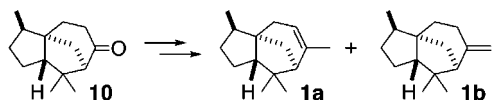
(9) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204. (c) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220. (d) Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199.

(10) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771.

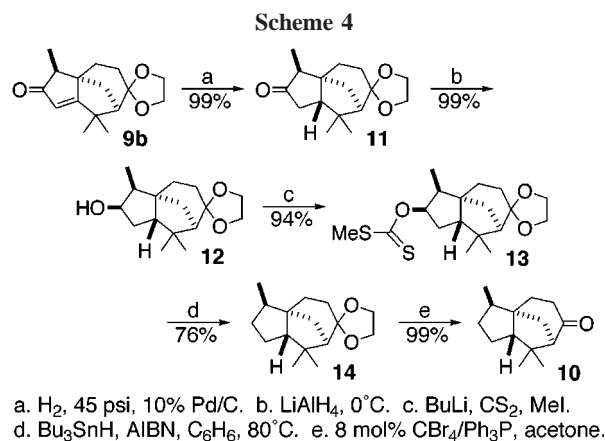
place smoothly and in high yield to provide the enones **9a/b**, thus demonstrating the novel applicability of this annulation process to the rapid and direct construction of more complex tricyclic systems from simple monocyclic substrates. The optimum yield of 95% for the cyclization to the cedrene skeleton was achieved using the soluble *n*-butyl methyl sulfide recommended by Sugihara.¹⁰ Additionally, despite the alternative polymer-supported sulfide providing a reduced yield of 80%, it should be noted that the reaction workup procedure with this solid-phase reagent was greatly facilitated by the ability of the resin-based species to sequester the unwanted cobalt residues, enabling removal of these byproducts by simple filtration. The amine *N*-oxide promoters tested were the commercially available dihydrate of trimethylamine *N*-oxide (TMANO·2H₂O) and the monohydrate of *N*-methyl morpholine *N*-oxide (NMO·H₂O); these milder room temperature processes also provided enones **9a/b** in high yields of 91% and 84%, respectively.

As shown in Scheme 3, enones **9a/b** were obtained as a mixture of stereoisomers in a ratio of 2:1, indicating that the relative stereochemistry present in the cyclization precursor **8a/b** (carried through from **6a/b**) had been transferred to the Khand product without alteration. At this stage, the diastereomers **9a/b** were separated by silica column chromatography and were independently characterized by X-ray crystallographic analyses; the major isomer **9a** featured the (C-15) methyl group, adjacent to the carbonyl, with the undesired (α) stereochemistry, with the minor isomer **9b** having the required methyl group (β) orientation.

After these assignments of relative stereochemistry with **9a** and **9b** had been made, it was now apparent that the specific ratio of olefin geometric isomers achieved through ethylenation of **5** was 2:1 (*Z*)-**6a**:(*E*)-**6b**. Thus, as perhaps anticipated under the standard Wittig reaction conditions employed for this olefination, the *Z*-product predominates. Work is currently underway to investigate alternative techniques in an endeavor to access enhanced proportions of the requisite *E*-isomer (**6b**) and a generally more useful isomer ratio, in relation to the synthesis of α -cedrene. Additionally and to address the same overall stereochemical issue with respect to the C-15 methyl group, conditions are presently being sought to allow efficient epimerization of the stereocenter possessing the α -methyl unit in **9a** (or the corresponding dihydro compound; see below) to, in turn, deliver the desired (β) orientation for access to the cedrenes **1a** and **1b**.



Previously reported syntheses of α -cedrene **1a** (and β -cedrene **1b**) have proceeded in two steps from cedrone **10**,^{2a,e,h} and we targeted this compound to complete our formal total synthesis of the natural products. Enone **9b** was subjected to palladium-catalyzed hydrogenation to give **11** in 99% yield (Scheme 4). This reaction was completely stereoselective, and once again, the relative stereochemistry



present in this reduced compound was determined by X-ray analysis. As shown, the newly introduced H-atom at the bridgehead position (C-7) has the required stereochemistry.

In due course, reduction of the carbonyl functionality of **11** was achieved almost quantitatively through treatment with lithium aluminum hydride. This reaction was also totally selective (at 0 °C) and afforded only one detectable alcohol isomer, tentatively assigned as compound **12**. In turn, the secondary alcohol **12** was reduced, via the xanthate ester **13**, following the well-established Barton–McCombie method;¹¹ the required deoxygenated product **14** was obtained in a yield of 76% when the intermediate **13** was treated with tributyltin hydride in the presence of a catalytic amount of AIBN initiator. Finally, the ketone protection was removed using a mild technique, discovered in our own laboratories, that involved the use of sub-stoichiometric quantities of carbon tetrabromide and triphenyl phosphine in acetone.¹² This furnished the target compound cedrone **10** in 99% yield, to establish a concise formal total synthesis of α - and β -cedrene, **1a** and **1b**.

In summary, we have shown that the structurally challenging tricyclic [5.3.1.0¹⁻⁵] carbon skeleton of α -cedrene **1a** (and β -cedrene **1b**) may be constructed in a direct and highly efficient manner, from a readily accessible and relatively simple monocyclic precursor, by the strategic use of a key intramolecular Khand cyclization reaction. The cyclopentenone intermediate so obtained was further elaborated to cedrone **10**, thus constituting a formal total synthesis of α - and β -cedrene. We also wish to note that compound **9a** was subjected to a sequence of reactions similar to those performed on **9b**. This resulted in the synthesis of *epi*-cedrene. A more detailed account of this work and further studies in this area will be disclosed in due course.

Acknowledgment. We are grateful to the Carnegie Trust for the Universities of Scotland for the award of a post-

(11) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574. (b) Hartwig, W. *Tetrahedron* **1983**, 39, 2609.

(12) (a) Johnstone, C.; Kerr, W. J.; Scott, J. S. *J. Chem. Soc., Chem. Commun.* **1996**, 341. (b) Caldwell, J. J.; Kerr, W. J.; Scott, J. S.; Shearer, G. C. Unpublished results.

graduate scholarship (M.M.). We also wish to thank Astra-Zeneca Pharmaceuticals for Strategic Research Funding (W.J.K.) and M. Pervez of the same company for the generous supply of some chemicals. We are also indebted to A. R. Kennedy for X-ray crystallography and to the EPSRC Mass Spectrometry Service, University of Wales, Swansea, for analyses.

Supporting Information Available: Experimental procedures and full characterization for compounds **3–8**, **9a**, **9b**, and **10–14**, as well as X-ray data for compounds **9a**, **9b**, and **11** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL016054A