ORGANIC LETTERS

2001
Vol. 3, No. 13
2041−2044

Stereocontrolled Construction of the A-Ring of Nitiol Using a Pauson–Khand Cycloaddition–Ring Fragmentation Strategy

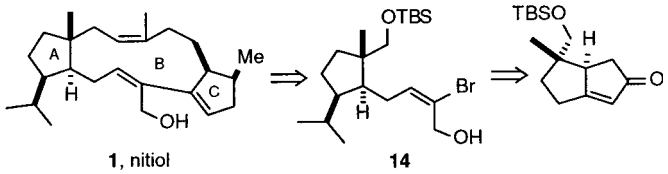
Michael S. Wilson and Gregory R. Dake*

Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z1

gdake@chem.ubc.ca

Received April 19, 2001

ABSTRACT



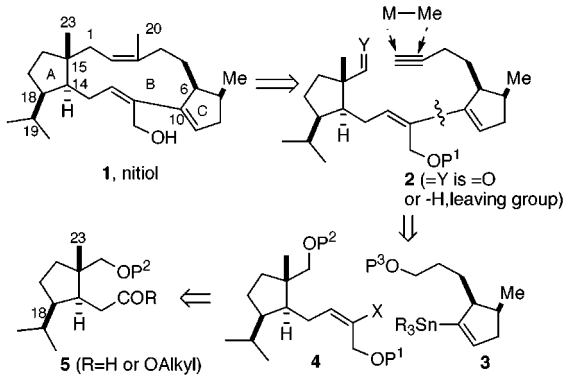
A stereocontrolled construction of the A-ring of nitiol (1) is presented. Key features in this approach are a diastereoselective Pauson–Khand cycloaddition and a Norrish type 1 fragmentation reaction.

Plants continue to be a rich source of compounds with diverse structures and medicinal activities.[1] The plant named *Gentianella (G.) nitida* (Gentianaceae) (common names "hercampuri" or "hircampure") is a biennial medicinal plant that grows in the Andes region and is used in traditional folk medicine. It is used to remedy hepatitis, as a cholagogue, and in the treatment of obesity. Extracts from this whole plant were purified several times, which led to the isolation of nitiol (**1**), a novel sesterterpenoid (Scheme 1).[2] Preliminary investigations have found that **1** acts as a potent enhancer of interleukin-2 in human T cell lines. In addition, because **1** has a structure distinctly different from those of known modulators of IL-2 gene expression, it represents a possible tool to probe for new signal transduction pathways that guide IL-2 gene transcription.

The structure of **1** was determined exclusively by NMR methods. Its structure is characterized by a tricyclic 5-12-5 ring system. A *trans* ring fusion was found between the A and B rings. A serious issue for chemical synthesis is the *cis* relationship between the isopropyl group on C18 and the C23 methyl group.

Chemical synthesis of **1** would serve to corroborate the structural determination made by Kawahara and co-workers. In addition, possibilities exist through chemical synthesis to fashion analogue structures of **1** that may exhibit enhanced biological activity.

Scheme 1. Analysis of Nitiol (**1**)



(1) Cordell, G. A. *Phytochemistry* **1995**, *40*, 1585. Houghton, P. J. *Chem. Ind. (London)* **1999**, 15. Paper, D. H. *Planta Med.* **1998**, *64*, 686.

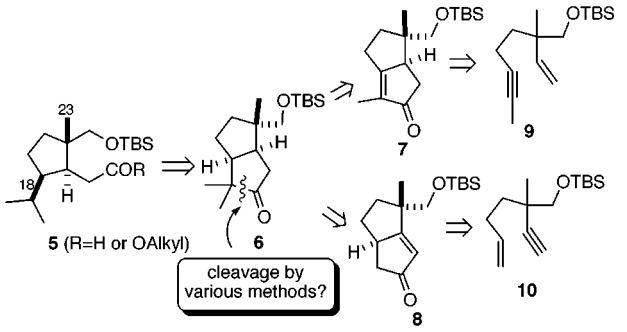
(2) Kawahara, N.; Nozawa, M.; Kurata, A.; Hakamatsuka, T.; Sekita, S.; Satake, M. *Chem. Pharm. Bull.* **1999**, *47*, 1344.

10.1021/ol016002l CCC: $20.00
Published on Web 06/07/2001

Analysis of the target structure **1** suggests a bifurcative synthetic approach (Scheme 1). Disconnection of the C1−C2 bond provides an uncyclized precursor **2**. In the synthetic direction, a number of possibilities, including a carbonyl addition reaction or a tandem carbometalation-S_N2 displacement, are expected to connect this crucial ring-forming bond. Methylmetalation of a terminal alkyne will be used to generate the necessary double bond geometry prior to the ring-closing reaction. Subsequent disconnection of the C10−C11 bond generates two halves, **3** and **4**. This bond is to be constructed using standard coupling protocols using a palladium(0)-catalyzed process. The vinyl halide of the "western" portion, **4**, will result from reduction, Horner−Wadsworth−Emmons olefination, and functional group manipulation of **5**. Cyclopentane **5**, the A-ring of nitiol, contains a key *cis* stereochemical relationship between the methyl and isopropyl groups in addition to what will become the *trans* ring junction of the A−B ring system.

A key issue in any construction of nitiol is the establishment of the configuration of the isopropyl moiety on the cyclopentane A ring. A classic method for setting stereochemistry is to use the bias of a cyclic system, after which the ring is broken open. A *trans*-hydrindane ring system may seem like an appropriate precursor to **5**. However, it is well established that reactions generating *trans*-hydrindanes bearing pendant methyl and isopropyl groups almost exclusively result in a *trans*-relationship between the methyl and isopropyl groups.[3] For this reason, our synthetic approach to **5** uses the conformational bias of a [3.3.0]bicyclooctane system to generate the required stereochemistry (Scheme 2). A

Scheme 2. Analysis of Fragment **5**

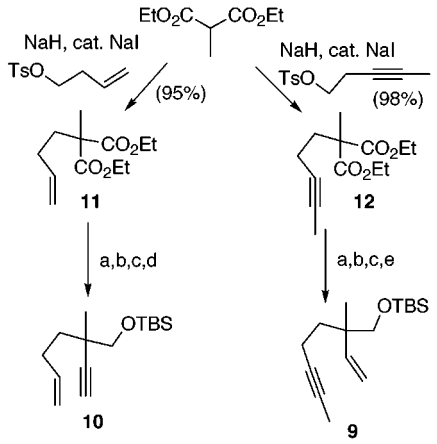


number of methods could be used for the fragmentation of the bicyclooctane, including a Baeyer−Villiger reaction, a fragmentation proceeding through an oxygen-based radical, or a Norrish type 1 process.

After the consideration of a number of options, it was determined that ketone **6** represented a key intermediate, whose construction would utilize the Pauson−Khand reaction.[4] Following several literature precedents, the larger substituent on the chain tethering the alkyne complex and the alkene should end up on the convex face of the bicyclooctene to minimize steric strain.[5] The main question was whether enough steric differentiation existed between a methyl and a CH_2OTBS group. If successful, this process would set up the relative stereochemistry for the A ring of nitiol. A benefit to this analysis was that **6** was thought to be obtainable from Pauson−Khand products **7** and **8**, which would derive from **9** and **10**, respectively. In this manner the importance of the position of the chirality center (the allylic or propargylic carbon) could be examined.

The construction of the enynes **9** and **10** was carried out in a straightforward manner (Scheme 3).[6] The formation of

Scheme 3[a]



[a] Reagents and conditions: (a) LAH, Et_2O (for **11**, 98%; for **12**, 96%); (b) Et_3N, TBSCl, DCM, rt (for **11**, 89%; for **12**, 94%); (c) DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C (for **11**, 87%; for **12**, 98%); (d) (i) Ph_3P, CBr_4, (ii) ^{n}BuLi, THF, −78 °C (65%); (e) CH_2Br_2, Zn, $TiCl_4$, $PbCl_2$ (86%).

2,2-disubstituted malonates **11** and **12** was carried out by alkylating diethyl methylmalonate with the appropriate tosylate using sodium hydride and catalytic sodium iodide in dimethylformamide.[7] Standard procedures (LAH reduction, TBSCl protection, oxidation, Corey−Fuchs or Nozaki reactions) were then used to generate the requisite enyne substrates **9** and **10**.

(3) (a) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339. (b) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872. (c) Attah-Poku, S. K.; Chau, F.; Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418.

(4) Brummond, K. M.; Kent J. L. *Tetrahedron* **2000**, *56*, 3263. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 1037. Schore, N. E. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, p 2.

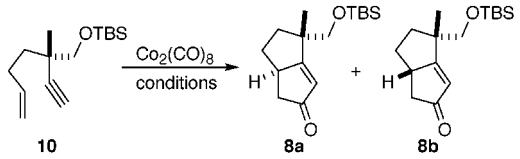
(5) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761. Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903. Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851.

(6) All new compounds have been satisfactorily characterized spectroscopically (NMR, IR, MS).

(7) For an enantioselective construction of the A-ring, pig liver esterase could be used to desymmetrize malonates **11** or **12**. As the remainder of the construction is stereoselective, this step would define the absolute stereochemistry for the construction of the western half of **1**. Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, T. *Tetrahedron* **1985**, *41*, 1347. Luyten, M.; Müller, S.; Herzog, B.; Keese, R. *Helv. Chim. Acta* **1987**, *70*, 1250. Toone, E. J.; Jones, J. B. *Tetrahedron: Asymmetry* **1991**, *2*, 1041.

These substrates were then submitted to various Pauson−Khand conditions (Tables 1 and 2).[8] Because we were

Table 1. Pauson−Khand Reaction of (Propargyl-Substituted) Enyne **10**

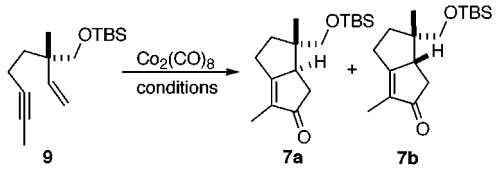


entry	solvent (and promoter)	T (°C)	t (h)	yield	dr (**8a**:**8b**)[a]
1	hexanes (none)	110	20	13%	1:1
2	CH_2Cl_2 (NMO)	25	12	31%	1:1
3	$ClCH_2CH_2Cl$ (C_6H_5SMe)	83	2	48%	1:1
4	water/dioxane (NH_4OH)	100	0.5	41%	1:1

[a] Ratios determined by integration of the ^1H NMR spectrum of the crude reaction mixture.

determining the viability of the overall approach, catalytic versions of the Pauson−Khand reaction have not been extensively examined, although these will be the subject of future investigations. Unfortunately enyne **10**, when treated with dicobalt octacarbonyl followed by a promoter, generated an equimolar mixture of diastereomers **8a** and **8b** in very low yields (Table 1). Investigations using **10** were halted as a result of these disappointing findings.

Table 2. Pauson−Khand Reaction of (Allylic-Substituted) Enyne **9**



entry	solvent (and promoter)	T (°C)	t (h)	yield	dr (**7a**:**7b**)[a]
1	CH_2Cl_2 (NMO)	25	12	40%	7.5:1
2	$ClCH_2CH_2Cl$ (C_6H_5SMe)	83	2	20%	nd
3	benzene (DMSO)	45	72	40%	7.7:1
4	$ClCH_2CH_2Cl$ ($C_6H_{11}NH_2$)	83	0.25	57%	5.7:1
5	water-dioxane (NH_4OH)	100	0.25	74%	6.3:1
6	DME[b] ($C_6H_{11}NH_2$)	60	18	84%	5.7:1
7	DME[c] (none)	70	18	25%	6.0:1

[a] Ratios determined by GC integration; nd = not determined. [b] 50 mol % $Co_2(CO)_8$ under a N_2 atmosphere. [c] 10 mol % $Co_2(CO)_8$ under a CO atmosphere.

Attention was then turned to **9**, which has its chirality center at the allylic position of the enyne. It was hoped that the proximity of the quaternary chirality center to the forming ring junction would enhance the diastereoselectivity of the Pauson−Khand reaction. In the event, submission of **9** to various Pauson−Khand conditions led to improved results (Table 2).

Running the reaction in methylene chloride using 6 equiv of *N*-methylmorpholine *N*-oxide (NMO) as a promoter gave a modest yield (40%), but happily the diastereoselectivity favoring **7a** was quite good (7.5:1) (entry 1), especially when considering that the stereodiscriminating event differentiates between a methyl and a CH_2OTBS group. Our focus turned to improving the yield of this process. Other solvents and promoters were surveyed. The use of thioanisole to promote the reaction in dichloroethane resulted in a very poor recovery of **7a** and **7b**, 20% (entry 2). The use of DMSO in benzene reestablished the overall yield of this process to 40%, with high stereoselectivity (entry 3). The use of Sugihara's conditions (cyclohexylamine in 1,2-dichloroethane or 3:1 2 M ammonium hydroxide in water and dioxane) very rapidly converted enyne **9** to the desired bicyclooctenes **7a** and **7b** in good yields (57−74%) with small diminishments in selectivity (5.7−6.3:1) (entries 4 and 5). Substoichiometric versions of the Pauson−Khand reaction worked well at 50 mol % loading of dicobalt octacarbonyl, but a lower loading of 10 mol % gave a poor yield (entries 6 and 7). The "ammonium hydroxide" method of Sugihara was satisfactory enough to continue the investigation of our planned route. At this time no modifications of the protecting group of **9** to other more sterically hindered groups that may result in improved stereoselection have been attempted.

The relative stereochemistries of **7a** and **7b** were determined by NMR methods. These compounds, which are easily separable by standard flash column chromatography on silica gel, were individually subjected to NOE experiments (Figure 1).

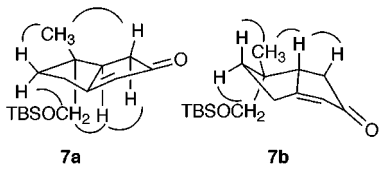
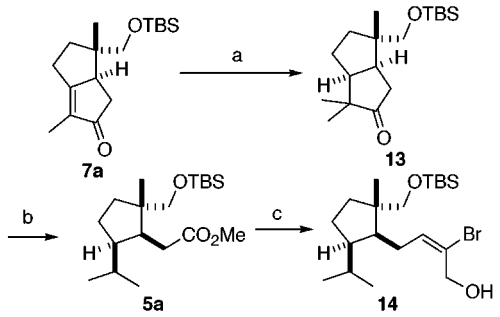


Figure 1. Selected NOE correlations of **7a** and **7b**.

Cyclopentenone **7a** was then subjected to conjugate reduction using lithium tri(*sec*-butyl)borohydride followed by quenching with methyl iodide to produce **13** in 83% isolated yield. The key α-carbonyl fragmentation reaction was performed by irradiating **12** with light from a 450-W Hanovia medium-pressure mercury lamp (Norrish type 1). To our delight, this procedure furnished trisubstituted cyclopentane **5a** in 50% yield (55% brsm). At this point the

(8) (a) No promoter: Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. (b) NMO: Adrio, J.; Rivero, M. R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2906. (c) C_6H_5SMe: Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771. (d) DMSO: Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220. (e) NH_4OH: Sugihara, T.; Yamada, M.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2601. (f) Krafft, M. E.; Bonaga, L. V. R.; Hirosawa, C. *J. Org. Chem.* **2001**, *66*, 3004.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) L-Selectride, (ii) CH_3I (83%) (b) hυ ($\geq$190 nm) quartz filter (50%, 55% brsm); (c) (i) DIBAL-H, CH_2Cl_2, (ii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2 (86%, two steps), (iii) $(CF_3CH_2O)_2POCHBrCO_2Et$ (**A**), KO^{t}Bu, 18-crown-6, THF, -78 °C (>97%, 14:1 *E*:*Z*), (iv) DIBAL-H, CH_2Cl_2 (97%).

ester functionality was converted to an aldehyde under standard conditions (reduction with diisobutylaluminum hydride; Moffatt−Swern oxidation; 86% for two steps). Treatment of the aldehyde with Kogen's Horner−Wadsworth−Emmons-type reagent **A**[9] generated the trisubstituted vinyl bromide with excellent yield (>97%) and stereoselectivity (*E*:*Z* = 14:1). Reduction of the ester to the alcohol using disobutylaluminum hydride proceeded normally (97%). Experimental support of the stereochemistry of the vinyl bromide was carried out by NOE NMR experiments on **14**. Specifically, NOE enhancements were observed between the two sets of allylic protons.

In summary, a short construction of an intermediate representing the A-ring of nitiol has been presented. The key strategic feature is the cleavage of a functionalized [3.3.0]bicyclooctane ring system to introduce the necessary stereochemical features at C18 and C23. Future work will include an enantioselective preparation of this A-ring component and efforts toward the natural product, nitiol.

Acknowledgment. We thank the University of British Columbia and the National Science and Engineering Research Council of Canada for the funding of this research. G.R.D. thanks Prof. Viresh Rawal and Prof. Edward Piers for stimulating discussions. M.S.W. thanks Prof. John Scheffer and his group for the use of photochemistry equipment and UBC for a McDowell Award.

Supporting Information Available: Spectroscopic data for **9** and **10** and experimental procedures and spectroscopic data for compounds **7**, **8**, **13**, and **5a**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016002L

(9) Tago, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 1975.