From Acyclic Precursors to Linear Triquinanes through a Diastereoselective One-Pot Process. A New Illustration of the Synthetic Power of Radical Cascades

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Received May 26, 1998

Because of the high versatility of the radical 5-*exo* (*trig* or *dig*) cyclization, polyquinanes have appeared as obvious targets in radical synthetic strategies.[1] Elegant studies by Curran, for instance, have relied on a five-membered templating ring, serving a tandem of 5-*exo* cyclizations, and have led to total syntheses of natural products such as hirsutene and silphiperfolene.[2] In view of obtaining linear triquinane frameworks expeditiously, the more ambitious triple cyclization strategy starting from acyclic precursors has also been challenged.[3] However, these latter approaches have shown little regio- and/or diastereoselectivity, yielding in most cases poorly functionalized substrates.

In addition to their unique structural features, our interest in the synthesis of triquinanes stems from the fact that the 5-*exo*-*dig* radical cyclization of (bromomethyl)dimethylsilyl ethers can be used as an efficient trigger for radical cascades;[4] notable was the highly diastereoselective one-pot formation of a diquinane.[5] Our initial attempts, however, were thwarted by the sensitivity of the unsaturated precursors toward hydrogen transfers from the initial vinyl radical.[6] We had, therefore, to modify our precursors and block the labile sites. The new generation of precursors includes bromomethylsilyl ethers **1** and **2**, and their radical cyclizations are reported herein (Scheme 1).

When submitted to the slow addition of Bu_3SnH in the presence of AIBN, and after a Tamao oxidation, precursor **1** furnished the tricyclo[3.0.1.0.1]nonane diol **7** as a single diastereomer. The formation of **7** results from a sequence of four cyclization steps, involving a rare 3-*exo*-*trig* radical cyclization,[7] whose driving force is the trapping of the α-cyclopropyl radical in a 5-*exo*-*dig* manner. The relative stereochemistry of **7** was determined through NOE measurements and originates from complete cis 1,3 asymmetric induction, which we have always encountered in the initial 5-*exo*-*dig*, 5-*exo*-*trig* tandem sequence (**1** → **3**).[5,6] This finding was clearly encouraging since it showed that the β-silyl radical **5** could be trapped in a diastereoselective manner. However, the low yield of **7**[8] suggested that the reaction might be cleaner if we used TMS-protected acetylenic partners. This turned out to be correct since the radical cyclization of **2** furnished the two adducts **4** and **10** in a much higher combined yield (89%). In this cascade, the R_1 TMS substituent exerts at least two functions. First, it probably slows down the 3-*exo*-*trig* so that the previously mentioned homoallyl radical **3** can be reduced to furnish cyclopentyl derivative **4**. Second, it readily engages in a 1,6-H transfer[9] with vinyl radical **6** to generate the α-silyl-stabilized radical **8**.[10] An additional 6-*endo*-*trig* radical cyclization followed by an unprecedented β-elimination of the trimethylsilyl radical[11] achieves the assembly of the pentacyclic structure **9** (also characterized as trimethylsilyl alcohol **10**), and the trimethylsilyl radical propagates the radical chain.[12] The stereochemistry of cyclopropane **9** was found to be identical to that of **7**, as confirmed through NOE measurements on **12**.

One point remained to be elucidated. The construction of the triquinane framework requires a [3 + 2] annulation step between the nucleophilic homoallyl radical **3** and an electron-deficient olefin.[13] This clearly implies a competition between an intermolecular addition step and an intramolecular 3-*exo*-*trig* ring closure. Work by Cekovic[14] suggested that the [3 + 2] annulation step should prevail, and indeed, adding 10 equiv of acrylonitrile proved rewarding (Scheme 2). After a Tamao oxidation, the 80:20 mixture of diastereomers **13** was isolated in 42% overall yield, accompanied by the cyclopropyl adduct **12**. The triquinane structure of the major α-CN diastereomer of **13** was confirmed by X-ray crystallography.[15] *An 11 elementary step process*[16] *is involved in the construction of these triquinanes.* Only incomplete stereocontrol during the [3 + 2] annulation step is responsible for the formation of the minor β-CN epimer of **13**. Heterocycle **11** could be isolated in 54% yield after chromatography on silica gel, and a treatment with methyllithium offered a variant of functionalization (alcohol **14**).

We then wanted to involve vinyl radical **6** in a 1,5-H transfer process. 1,5-H transfers are generally favored over 1,6-H transfers.[17] Moreover, Curran has shown that the OTBS moiety is a very good activating group for hydrogen transfers from a vinyl radical.[18] Thus, we studied the behavior of OTBS ether **15** under radical cyclization conditions (Scheme 3), and we obtained hydrindane **17** as a single *E*,*E* diastereomer, whose stereochemistry was established through NOE experiments. The formation of **17** presumably results from the previously described radical cascade, followed by the expected 1,5-H transfer and the very fast

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(5) Journet, M., Smadja, W.; Malacria, M. *Synlett* **1990**, 320.

(6) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085.

(7) The high reversibility of the formation of α-cyclopropyl radicals is well established and has been usually overcome using electronic effects or by introducing a fast irreversible step, such as a fragmentation. For recent references, see: (a) Srikrishna, R.; Viswajanani, R.; Reddy, T. J.; Vijaykumar, D.; Kumar, P. P. *J. Org. Chem.* **1997**, *62*, 5232. (b) Ferjancic, Z.; Saicic, R. N.; Cekovic, Z. *Tetrahedron Lett.* **1997**, *38*, 4165. (c) Weng, W.-W.; Luh, T.-Y. *J. Org. Chem.* **1993**, *58*, 5574. (d) Journet, M.; Malacria, M. *J. Org. Chem.* **1994**, *59*, 718.

(8) Minor products were also observed on the TLC of the crude product.

(9) For a related 1,6-H transfer, see: Bogen, S.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 5037.

(10) Zhang, S.; Bordwell, F. G. *J. Org. Chem.* **1996**, *61*, 51.

(11) A trimethylsilyl group at the β-position stabilizes an alkyl radical by 2.6−2.8 kcal·mol^{-1}. Therefore, β-elimination is not a favorable process, and to the best of our knowledge has never been observed; see: Hwu, J. R.; Furth, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 8834.

(12) The reaction cannot be run with a catalytic amount of Bu_3SnH (25 mol %); however the trimethylsilyl radical (E(Si−H) = 95 kcal·mol^{-1}) resulting from the β-scission presumably does react with Bu_3SnH to generate the stannyl radical (E(Sn−H) = 74 kcal·mol^{-1}); see: Chatgilialoglu, C. *Chem. Rev.* **1995**, *95*, 1229.

(13) (a) Barton, D. H. R.; da Silva, E.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 285. (b) Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1989**, *13*, 2501. (c) Feldman, K. S.; Berven, H. M.; Weinreb, P. H. *J. Am. Chem. Soc.* **1993**, *115*, 11364.

(14) Saicic, R. N.; Cekovic, Z. *Tetrahedron* **1992**, *48*, 8975. See also: Srikrishna, A.; Danieldoss, S. *J. Org. Chem.* **1997**, *62*, 7863.

(15) The authors have deposited atomic coordinates for **13** with the Cambridge Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, UK.

(16) This cascade starts with the dissociation of AIBN and ends with the β-elimination of the trimethylsilyl radical.

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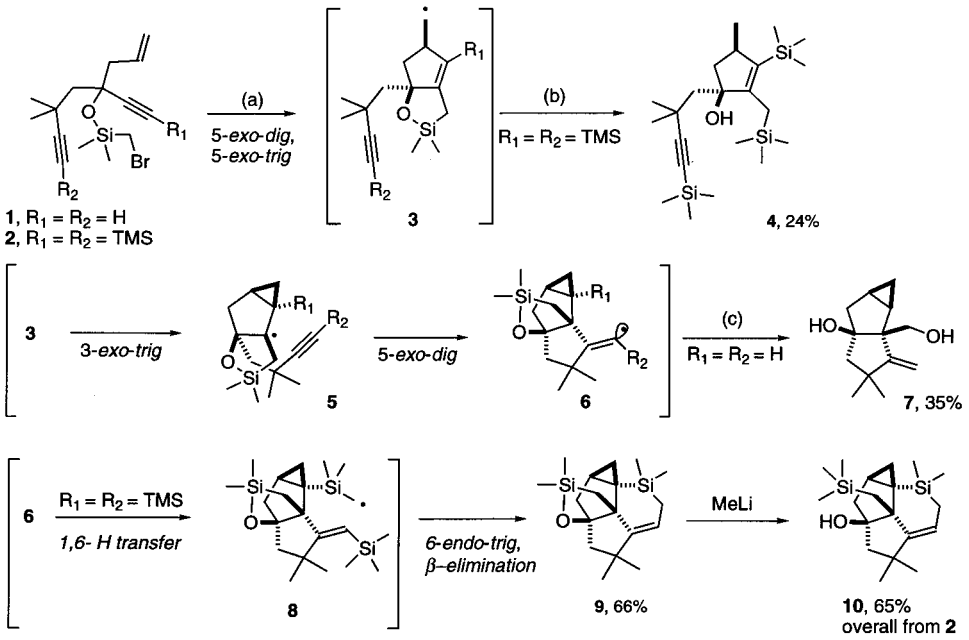
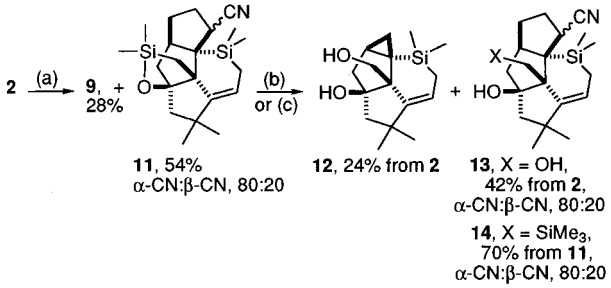
S0022-3263(98)00978-5 CCC: $15.00
Published on Web 09/11/1998

Scheme 1[a]



[a] Key: (a) Bu_3SnH, AIBN; (b) (1) Bu_3SnH, (2) MeLi: (c) (1) Bu_3SnH, (2) $KHCO_3$, H_2O_2, THF−MeOH.

Scheme 2



(a) Bu_3SnH, 10 equiv ; (b) MeLi; (c) Tamao oxidation.

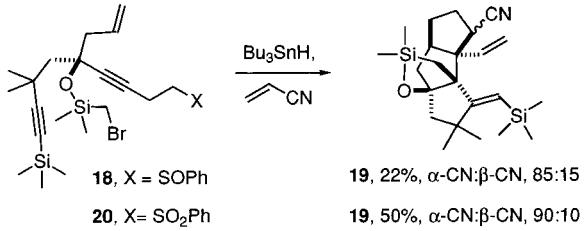
Scheme 3[a]

[a] Key: (a) Bu_3SnH, AIBN, (b) (1) Bu_3SnH, (2) MeLi.

rearrangement of the α-cyclopropyl radical **16**, confirming the validity of our design.

We next sought to obtain the triquinane framework without an additional ring. We focused on an approach ending with a favorable 1,5-H transfer and followed by the *β*-elimination of a suitable leaving group, thus avoiding telomerization of the last radical intermediate with acrylonitrile[19] and giving a clear-cut route to the cascade. Sulfoxide **18** and sulfone **20** appeared as good candidates (Scheme 4). The arylsulfinyl group is indeed very prone to *β*-elimination; however, it couples rapidly to give a thiosulfonate adduct,[20] and it does not carry on the radical chain. Therefore, we ran the radical cyclization of **18** with 1 equiv of AIBN. As anticipated, vinyltriquinane **19** was isolated as a 85:15 mixture of diastereomers; however, the conversion

Scheme 4



of the reaction was low (around 50% of starting material **18** remained unaltered). We then turned to sulfone **20**, which turned out to be the precursor of choice. The radical cyclization required 2 equiv of tributyltin hydride,[21] but only a catalytic amount of AIBN, and furnished **19** in 50% overall yield as a 90:10 mixture of diastereomers. Further treatment with MeLi provided alcohol **21** in 21% overall yield.

In conclusion, we have demonstrated that the highly diastereoselective synthesis of functionalized linear triquinane frameworks from acyclic precursors is possible through a radical cascade. The substitution pattern of these triquinanes can be conveniently tuned by using a 1,5- or a 1,6-hydrogen transfer step at the same stage of the final vinyl radical. These 10 or 11 elementary step radical cascades are cleanly terminated by the *β*-elimination of a trimethylsilyl or an arylsulfonyl group, which carries on the radical chain. We are now focusing on the application of this chemistry toward the synthesis of complex molecules of biological and theoretical relevance.

Acknowledgment. The authors thank Dr. J. J. Barieux of Elf Atochem and the Elf Atochem Co. for their financial support. The authors are greatly indebted to Dr. J. Vaissermann, Université P. et M. Curie, for carrying out the X-ray structure of α-CN **13**.

Supporting Information Available: Typical procedures, summary of characterization data for **1**, **2**, **4**, **7**, **9**−**15**, and **17**−**21**, X-ray structure of α-CN **13**, NMR spectra of **19** and **21**, and NOE spectra for **12** (23 pages).

JO9809783

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