Pergamon

Tetrahedron Letters, Vol. 36, No. 49, pp. 8921-8924, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01918-9

Towards a Tandem-Radical Macrocyclization-Transannular Cyclization Approach to Steroids: Transannular Cyclizations of a Macrocyclic Core

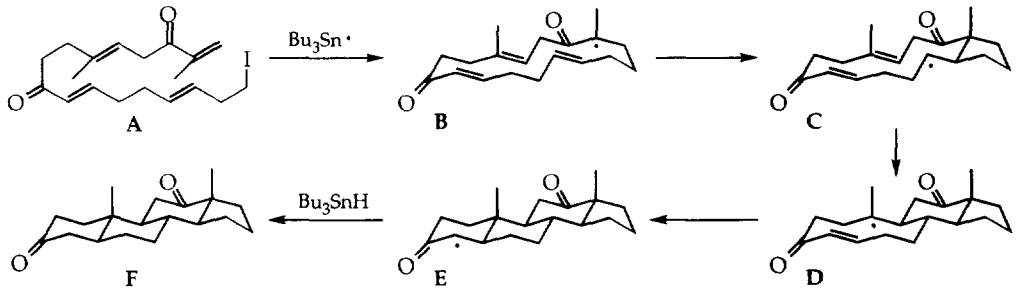
Ullrich Jahn and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

Abstract: *The triple transannular radical cyclization of 1-cyano-5-methyl-1-phenylseleno-8-hydroxy-4,9,13-cycloheptadecatriene (**1a**) provided a product **2** possessing the steroid ring skeleton of unassigned configuration in 4% isolated yield. A high yielding transannular cyclization of the related diene lacking the $\Delta^{4,5}$double bond identifies the second cyclization as the Achilles heel of the triene cyclization.*

The elucidation of the biosynthesis of steriods via enzymatic cationic tetracyclization of 2,3-oxidosqualene[1] has inspired organic chemists over the last three decades to construct the steroid skeleton by polycyclization cascades.[2] The recent rapid development of radical cyclization methods[3] has generated renewed[4a,b] interest in cascade radical approaches to the steroid skeleton.[4c-f]

In this letter, we report the initial results of a new tandem radical approach to the steroid skeleton (Scheme 1). Due to anticipated problems connected with 6-*exo* cyclizations in acyclic systems (low rates, competing [1,5]-hydrogen transfer), we decided to explore the feasiblity of transannular 6-*exo* cyclizations of macrocyclic radicals. The plan calls for radical macrocyclization (**A** → **B**), followed by a contractive transannular cyclization cascade[5] beginning with the formation of the D-ring by a radical 5-*exo* cyclization (**C**). This is followed by two 6-*exo* cyclizations to give **F** via **D** and **E** (Scheme 1).

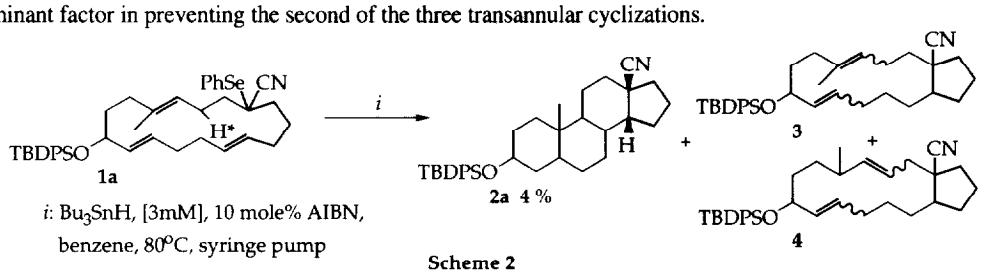


Scheme 1

About two years ago, H. Yu prepared **A** and found that a very complex mixture was formed upon standard syringe pump addition of tin hydride.[6] Good precedent for the radical macrocyclization exists,[4e,5,7] so we concluded that the problem must rest in one of the transannular cyclizations. The transannular radical cyclization steps have now been examined separately starting from related macrocyclic precursors **1a,b**, and a likely reason for the failure of the cascade in Scheme 1 has been identified.

Transannular Cyclization Results: The transannular radical cyclizations of macrocycles **1a,b** were carried out with tributyltin hydride at fixed concentrations. At high [0.5M] concentration, the macrocycle **1a** yielded only the directly reduced diastereomers (not shown, PhSe replaced by H) in a 1.3 : 1 ratio. At low [3mM] concentration, a complex reaction mixture was obtained (Scheme 2). Repeated separation by hplc provided 4% yield of a single tetracyclic product **2a** possessing a cis CD-ring junction as judged by comparison of spectral properties with **5a-d** (see below). As far as we know, this is the first example of a triple transannular radical cyclization. The main amount of material could be assigned as monocyclized products like **3** and **4**.

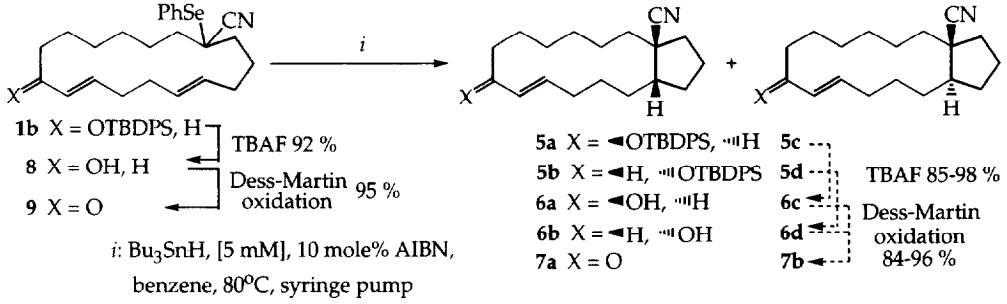
The extensive double bond migration/isomerization indicates that [1,5]-hydrogen transfer (see H* in **1a**) is the dominant factor in preventing the second of the three transannular cyclizations.



Scheme 2

To prove the occurence of the 5-*exo* cyclization, we studied cyclizations of macrocycle **1b** (Scheme 3) saturated in the $\Delta^{4,5}$ position and lacking a methyl group (to reduce the number of stereoisomeric products).[8] At [5 mM] tin hydride concentration, we obtained the cyclized products **5a-d** in 66 % isolated yield in a 3.9 : 3.4 : 1.2 : 1 diastereomeric ratio (Table 1) along with 3 % of the reduced product (not shown) and some minor unidentified products. This shows the viability of the first of the three transannular cyclizations.

The stereochemical outcome of the cyclization was established as follows. Separation by hplc provided the pure individual diastereomers **5a-d**. Deprotection of the TBDPS group yielded the corresponding alcohols **6a-d**. The major diastereomer **6a** gave suitable crystals for an X-ray analysis (Figure 1). This revealed a cis ring junction of the bicycle with the hydroxy group syn to the nitrile. Dess-Martin oxidation of the diastereomers **6a** and **6b** to a single ketone **7a** proved that both major cyclization diastereomers **5a** and **b** possess cis ring junction. Alcohols **6c** and **6d** each provided **7b**. This 3.3 : 1 cis preference is opposite to the trans CD configuration found in most naturally occuring steroids.



Scheme 3

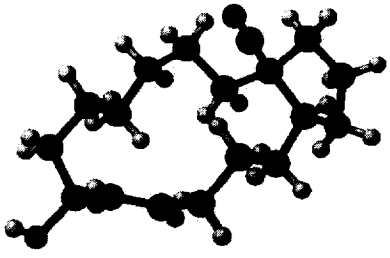


Figure 1: X-ray structure of **6a**

Table 1: Isolated Yields and Diastereomeric Ratios of the Cyclization Products **5**, **6** and **7**[a]

X	yield	diastereomeric ratio a : b : c : d
-OTBDPS	66	3.9 : 3.4 : 1.25 : 1
-OH	73	4.3 : 3.8 : 1.5 : 1
=O	84	4.3 : 1[b]

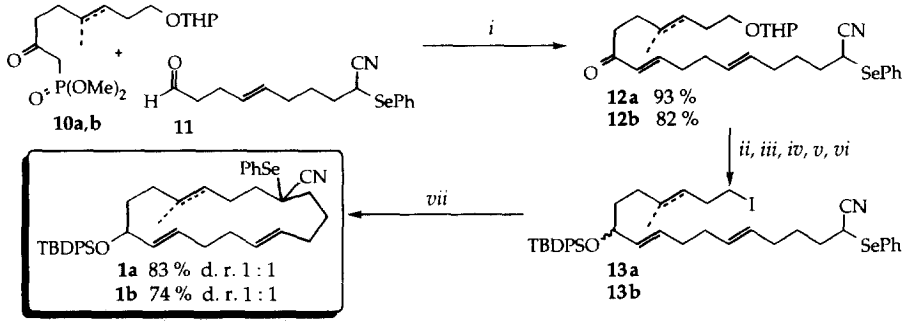
a: after hplc; b: determined by ^{1}H nmr

To investigate the influence of remote substituents on the transannular cyclization, we prepared the derivatives **8** and **9** by successive TBAF-induced deprotection and Dess-Martin oxidation of **1b**. Transannular radical cyclization of **8** gave the 5-*exo* cyclized products **6a-d** (Table 1) in the same cis/trans ratio of 3.2 : 1. The diastereomers **6a-d** were identical to those obtained before by TBDPS-deprotection of **5a-d**. In contrast, the cyclization of the macrocyclic ketone **9** gave a higher cis/trans ratio (4.3 : 1) of **7a, b**.

Preparation of the Macrocycles: The synthesis of the macrocycles **1a,b** is outlined in Scheme 4.[9] The approach provides the flexibility to make structural changes necessitated by the transannular cyclization results without changing the strategy. Details on the synthesis of the starting macrocycles will be given in a subsequent full account.

The Masamune-Roush protocol[10] proved to be most reliable for the assembly of the skeleton **12** from β-ketophosphonates **10**[9] and aldehyde **11**.[9] Luche reduction of **12** was necessary to circumvent problems in the macrocyclization. Among several protecting groups tried, the TBDPS group turned out to be superior in the subsequent steps. Finally, conversion of the THPO group into the iodide completed the synthesis of the macrocyclization precursors **13a** and **b**.

Provided that 2 equiv of LiHMDS was used, the macrocyclization of **13** proceeded smoothly between –78 and –20°C at [1 mM] to give macrocycles **1a, b** as about 1 : 1 diastereomeric mixtures. With only one equiv of base, yields did not exceed 40 % even after prolonged reaction times at room temperature. The TBDPS group had a beneficial effect on the course of the macrocyclization; pivaloyl and MEM-protecting groups gave much lower yields.



i: LiCl, i-Pr_2NEt, CH_3CN, 20°C; *ii*: $NaBH_4$, $CeCl_3$, MeOH, –20 - 0°C, **a** 88 %, **b** 98 %; *iii*: TBDPSCl, imidazole, CH_2Cl_2, 20°C, **a** 91 %, **b** 98 %; *iv*: PPTS, EtOH, 50°C, **a** 77 %, **b** 80 %; *v*: MsCl, NEt_3, CH_2Cl_2, –20°C, **a** 94 %, **b** 94 %; *vi*: NaI, $CaCO_3$ (cat.), acetone, **a** 96 %, **b** 96 %; *vii*: 2.2 LiHMDS, [1mM] THF, –78 - –20°C.

Scheme 4

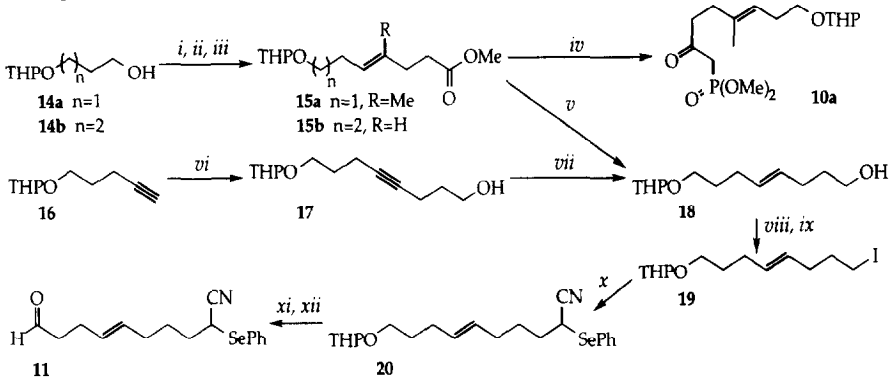
In summary, we have demonstrated that intramolecular alkylations of 2-(phenylseleno)acetonitriles are a valuable strategy to assemble macrocyclic cores. The subsequent transannular 5-*exo* cyclizations of 17-membered radicals occur smoothly and with moderate cis selectivity. In contrast, the ensuing transannular 6-*exo* cyclizations to isolated double bonds are severely limited by competing transannular [1,5]-hydrogen transfer from an allylic position. The investigation of appropriately modified systems is underway.

ACKNOWLEDGEMENTS: We thank the National Institutes of Health for funding, and Dr. S. J. Geib for solving the crystal structure. U. J. thanks the German Academic Exchange Service for a postdoctoral fellowship.

References and Notes

1. Bohlmann, R.; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 582.
2. a) Cationic: Sutherland, J. K. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds.; Pergamon Press Oxford, 1991, Vol. 3, 341. b) Carbopalladation: Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323.

3. a) Curran, D. P. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds.; Pergamon Press Oxford, 1991, Vol. 4, 715, 779. b) Giese, B. in *Houben-Weyl - Methoden der Organischen Chemie*, Regitz, M.; Giese, B. Eds.; Georg-Thieme-Verlag Stuttgart, 1989, Bd. E19a. c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
4. a) Julia, M.; Surzur, J.-M.; Katz, L. *Bull. Soc. Chim. Fr.* **1964**, 1109. b) Breslow, R.; Olin S. S.; Groves, J. *Tetrahedron Lett.* **1968**, 1837. c) Zoretic, P. A.; Weng, X.; Caspar, M. L. *Tetrahedron Lett.* **1991**, *32*, 4819. d) Wu, S. H.; Journet, M.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 8601. e) Begley, M. J.; Pattenden, G.; Smithies, A. J.; Walter, D. S. *Tetrahedron Lett.* **1994**, *35*, 2417. f) Chen, L. G.; Gill, G. B.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 2593.
5. For radical macrocyclization/transannular cyclization sequences see: a) Porter, N. A.; Chang, V. H. T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554. b) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843. Tandem transannular cyclizations: reference 4e, and c) Myers, A. G.; Condronski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057.
6. Yu, H. Ph. D. Thesis, University of Pittsburgh, 1994. A related failure is reported in reference 4e. In this reaction, the proposed order of the transannular cyclizations is reversed, and the last cyclization forming rings C/D appears to be 5-*endo*.
7. For radical macrocyclizations see: ref. 5, and a) Ryu, I.; Nagahara, K.; Yamazaki, H.; Tsunoi, S.; Sonoda, N. *Synlett* **1994**, 643 and ref. cited therein. b) Feldman, K. S.; Berven, H. M.; Romanelli, A. L.; Parvez, M. *J. Org. Chem.* **1993**, *58*, 6851 and ref. cited therein. c) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *Tetrahedron* **1992**, *48*, 3413. d) Hitchcock, S. A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1323.
8. Every cyclization experiment was accompanied by an experiment at [0.5M] tin hydride to identify the reduced products and obtain information about the ease of cyclization via the extent of cyclized products. **1b** gave 67 % reduced products as a 1.3 : 1 diastereomeric mixture along with 15.6 % of cyclized diastereomers **5a - d** in a ratio of 5 : 4 : 1 : 1.
9. Compounds **10a** and **11** were synthesized according to Scheme 5. The saturated β-ketophosphonate **10b** was prepared by Baeyer-Villiger oxidation of suberone,[11] phosphonomethylation (conditions as *iv* in Scheme 5) and THP-protection (not shown).



i: $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, **a** 89 %, **b** 92 %; *ii*: a 2-bromopropene, Mg, THF, 0 - 20°C, 73 %, **b** $H_2C{=}CHMgBr$, THF, –40 - –20°C, 74 %; *iii*: $MeC(OEt)_3$, EtCOOH (cat.), 110 °C, **a** 72 %, **b** 75 %; *iv*: 2 $MePO(OMe)_2$, 2 BuLi, THF, –78 - –10°C, 78 %; *v*: $LiAlH_4$, THF, 40°C, 84 %, *vi*: n-BuLi, oxetane, $BF_3{\cdot}OEt_2$, THF, –78 - –50°C, 96 %; *vii*: Li, liq. NH_3, reflux, 75 %; *viii*: MsCl, NEt_3, CH_2Cl_2, –20°C, 96 %; *ix*: NaI, Na_2CO_3 (cat.), molecular sieves 4Å, methyl ethyl ketone, 50°C, 96 %; *x*: $PhSeCH_2CN$, LiHMDS, THF, –78 - –20°C, 73 %; *xi*: TsOH (cat.), MeOH, 20°C, 97 %; *xii*: $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 79 %.

Scheme 5

10. Blanchette, M. A.; Choi, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
11. Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253.

(*Received in USA* 12 *September* 1995; *revised* 28 *September* 1995; *accepted* 29 *September* 1995)