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Published on Web 06/14/2008

Rapid and Enantioselective Synthetic Approaches to Germanicol and Other Pentacyclic Triterpenes

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Abstract: Two exceedingly short synthetic routes to the key intermediate **2** for the synthesis of the pentacyclic triterpene germanicol **1** have been developed. In the first, the (*S*)-epoxide of farnesyl bromide is transformed in just three steps to the tetracyclic intermediate **7**, which is converted to chiral **2** by treatment with polyphosphoric acid. The second synthetic route to **2** involves the coupling of the (*S*)-epoxide **8** with vinyl iodide **9** to give **10** and two-stage acid-catalyzed cyclization of **10** to form **2**. During the course of this work we have also discovered a very unusual intramolecular 1,5-proton shift from a carbocation to a C−C double bond. The details of the process have been confirmed by ^{2}H-labeling experiments.

In 1970 the combined research groups of R. E. Ireland and W. S. Johnson described a now classic synthesis of the pentacyclic triterpenoid germanicol **1** in racemic form.[1] The difficulty of accessing the racemic structure can be readily appreciated from the facts that (1) ca. 32 steps were required and (2) only a 0.1% overall yield was reported. Because of such difficulty shorter, more efficient, and enantioselective syntheses of pentacyclic triterpenoids have remained a formidable challenge to synthesis. The not unreasonable possibility that the various parent pentacyclic triterpenes are biosynthesized from (*S*)-2,3-oxidosqualene in a single step[2] underscores the disparity between conventional multistep synthesis and enzymically controlled biosynthesis. Nonetheless, until recent years there has not been significant progress in this area because of the complexity of dealing with the combination of numerous angular methyl groups and the large steric repulsions that they cause. We disclose herein the development of a short and quite efficient enantiocontrolled route to germanicol that is based on methodology that has recently been devised for targets of this sort.[3,4] Our specific plan was directed at the chiral pentacyclic target **2**, the racemic form of which was used by the Ireland and Johnson groups to synthesize (±)-germanicol. Two short and efficient enantioselective routes to the pentacycle **2** have emerged, as detailed herein.

The first synthetic pathway to **2** utilizes epoxide-initiated cation−olefin polyannulation and starts with the readily available chiral building block **3**, which was obtained from farnesyl acetate as described earlier.[5] Coupling of **3** via the corresponding bromide with the lithio derivative of the silyl imine **4** provided the known acyl silane **5**[6] (Scheme 1). The epoxy triene **6** was assembled stereoselectively from **5**, 2-propenyllithium, and 3-methoxybenzyl bromide in a single step by a one-flask, three component coupling involving (1) nucleophilic addition of 2-propenyllithium to the carbonyl group of **5**, (2) Brook rearrangement, and (3) 3-methoxybenzylation of the resulting allylic lithium intermediate.[7] The triene **6** was treated with 1.5 equiv of $MeAlCl_2$ in CH_2Cl_2 at −94 °C for 30 min to effect cationic cyclization. After silylation with *t*-butyldimethylsilyl chloride (TBSCl), the tetracyclic ketone **7** was obtained. Exposure of this product to polyphosphoric acid at 23 °C for 30 min afforded directly the target pentacycle **2**, spectroscopically identical with the Ireland−Johnson product. It is evident that the synthesis outlined in Scheme 1 represents a major advance over the original route to **2** in terms of brevity, efficiency, and enantiocontrol.

The second effective approach to the synthesis of germanicol via **2** is outlined in Scheme 2. The chiral epoxy diene **8**, $[\alpha]_D^{23} = +8.7$ ($CHCl_3$), obtained from the (*S*)-epoxide of geraniol[5] by oxidation with activated MnO_2 in C_6H_6 at 23 °C followed by Wittig condensation with methylenetriph-

(1) Ireland, R. E.; Baldwin, S. W.; Dawson, D. J.; Dawson, M. I.; Dolfini, J. E.; Newbould, J.; Johnson, W. S.; Brown, M.; Crawford, R. J.; Hudrlik, P. F.; Rasmussen, G. H.; Schmiegel, K. K. *J. Am. Chem. Soc.* **1970**, *92*, 5743–5746.

(2) Kürti, L.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* , Submitted for publication.

(3) (a) For recent enantioselective synthesis of erythrodiol, oleanolic acid, and β-amyrin, see Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873–8874. (b) Huang, A, X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003. (c) For a very short synthesis of tritrepene onorcerin, see Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291.

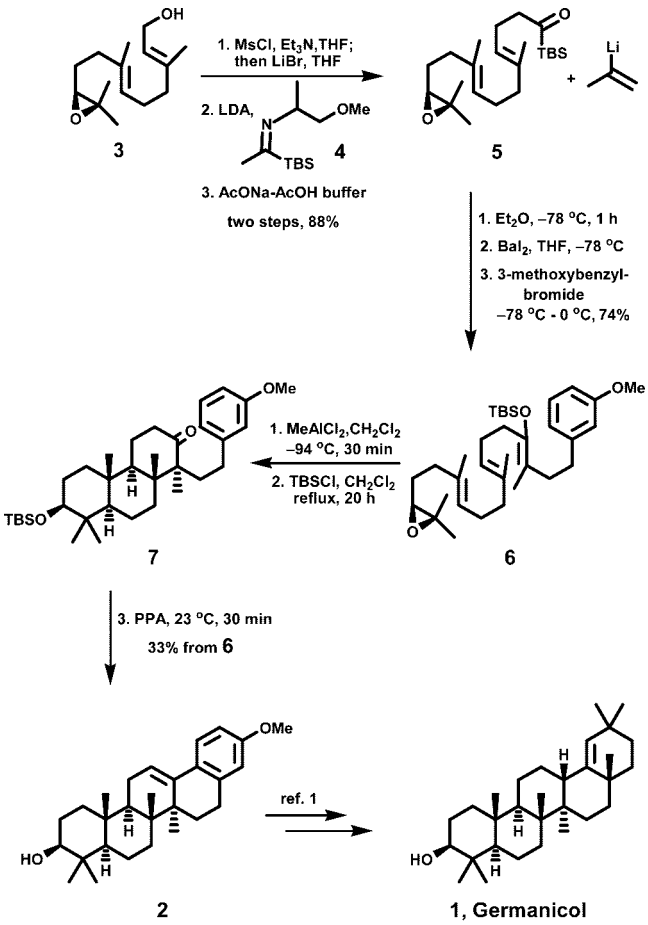
(4) For a recent review of epoxide-initiated cyclization, see Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730–4756.

(5) (a) Corey, E. J.; Noe, M. C.; Shieh, W-C. *Tetrahedron Lett.* **1993**, *34*, 5995–5998. (b) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741–8744. (c) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211–3214. (d) Huang, J.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3455–3458.

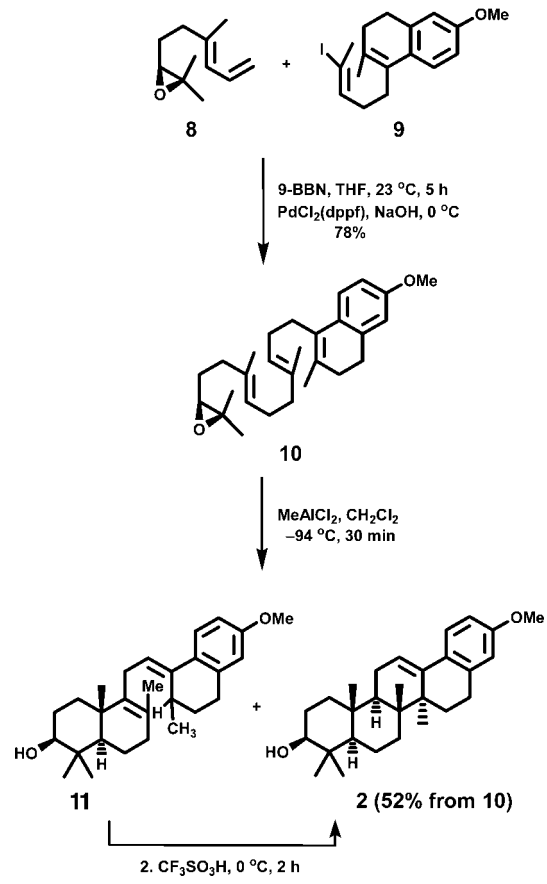
(6) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765–8766.

(7) (a) For other examples of this sequence, see Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927–9928. (b) Corey, E. J.; Luo, G.; Lin, L. S. *Angew.Chem., Int. Ed.* **1998**, *37*, 1126–1128. (c) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215–3216. (d) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291.

Scheme 1



Scheme 2



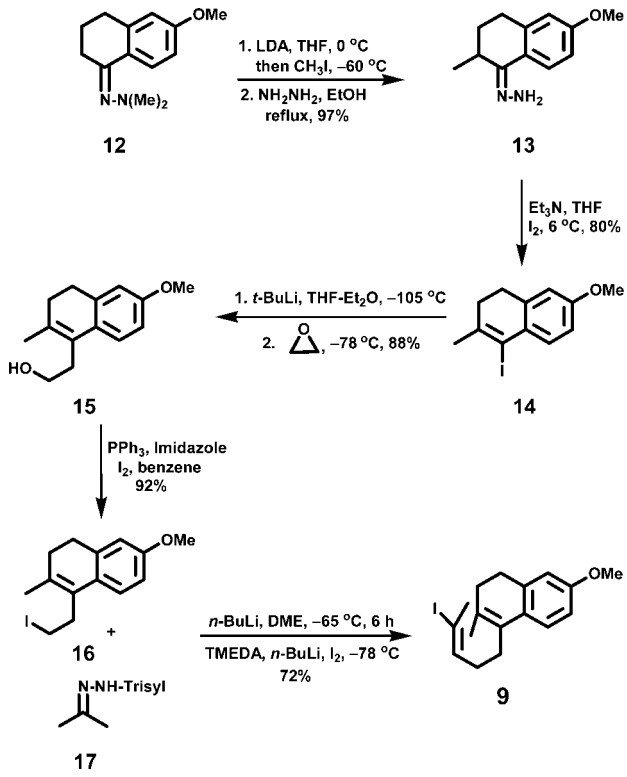
enylphosphorane in THF (85% yield over two steps), was coupled with the iodo diene **9** using Brown−Suzuki−Miyaura methodology[8] to form stereoselectively in a single step the chiral epoxy triene **10** in good yield. In detail, the epoxy diene **8** was hydroborated with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF and the resulting primary, homoallylic-substituted 9-BBN was (without isolation) allowed to react with vinyl iodide **9** in the presence of 5 mol % of $PdCl_2$−diphenylphosphinoferrocene (dppf)[9] and aqueous sodium hydroxide at 0 °C[10] to give the epoxy triene **10** in 78% overall yield. Exposure of **10** to 3.0 equiv of $MeAlCl_2$ in CH_2Cl_2 at −94 °C for 30 min produced a mixture of the isomeric cyclization products **11** and **2** in a ratio of 3:7, respectively, as determined by ^1H NMR analysis. This mixture was smoothly converted to pure **2** by further treatment with a solution of triflic acid (5 equiv) in CH_2Cl_2 at 0 °C for 2 h. The formation of **2** from **11** by treatment with triflic acid can occur by H^+-catalyzed transposition of the exocyclic, 11,12-double bond to the endocyclic, 12,13-location. Pentacycle **2** obtained in this way was completely identical (^1H NMR, ^{13}C NMR, TLC, and optical rotation) with a sample of **2** produced by the sequence of reactions outlined in above Scheme 1.

The synthesis of the *E*-vinyl iodide **9**, which served as the second building block for the synthesis of **2** shown in (Scheme 2), was carried out by the sequence shown in Scheme 3. The *N*,*N*-dimethylhydrazone **12**, prepared in 99% yield from 6-methoxy-1-tetralone and 1,1-dimethylhydrazine and HOAc in C_6H_6 at reflux, was α-methylated by sequential treatment with 1.0 equiv of LDA in THF at 0 °C followed by methyl iodide[11] and then transformed into the hydrazone **13** by heating with H_2NNH_2 in EtOH at reflux.[12] Slow addition of **13** to a solution of iodine in THF at 6 °C provided the bicyclic vinyl iodide **14**.[13] Bis-homologation of **14** to form the iodide **16** was accomplished by the sequence: (1) lithiation followed by reaction with ethylene oxide to give the primary alcohol **15** (88%) and (2) reaction of **15** with Ph_3P-I_2−imidazole (92% of **16**). Alkylation of **16** with the dilithio derivative of acetone 2,4,6-triisopropylbenzenesulfonyl (trisyl) hydrazone followed by a further deprotonation with *n*-BuLi−tetramethylethelenediamine (TMEDA) afforded a vinyllithium derivative (along with N_2 and trisyl anion), which upon iodination produced stereoselectively[14] the required *E*-vinylic iodide **9** (72%).[10,14]

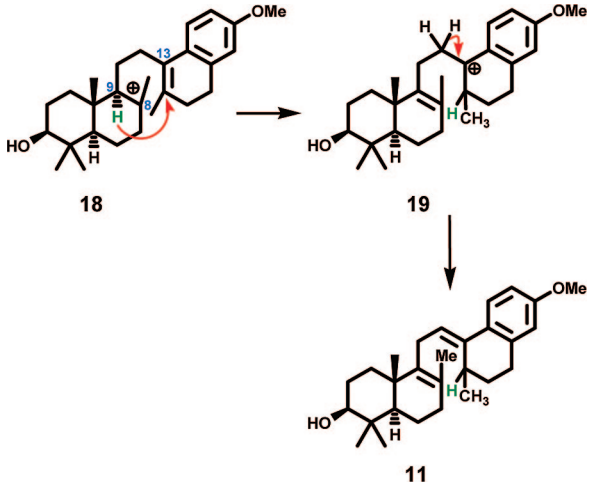
The formation of the coproduct **11** along with pentacycle **2** in the cyclization of **10** (Scheme 2) has been investigated

(8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
(9) (a) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *20*, 1871–1874. (b) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765–7777.
(10) Corey, E. J.; Lee, J.; Roberts, B. E. *Tetrahedron Lett.* **1997**, *38*, 8919–8920.
(11) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *17*, 3–6.
(12) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677–681.
(13) (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron Lett.* **1983**, *24*, 1605–1608. (b) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470–476. (c) This preparation of **14** was first carried out in these laboratories by Daniel Lieberman, Ph. D. dissertation, Harvard University, 1986.
(14) Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256–257.

Scheme 3

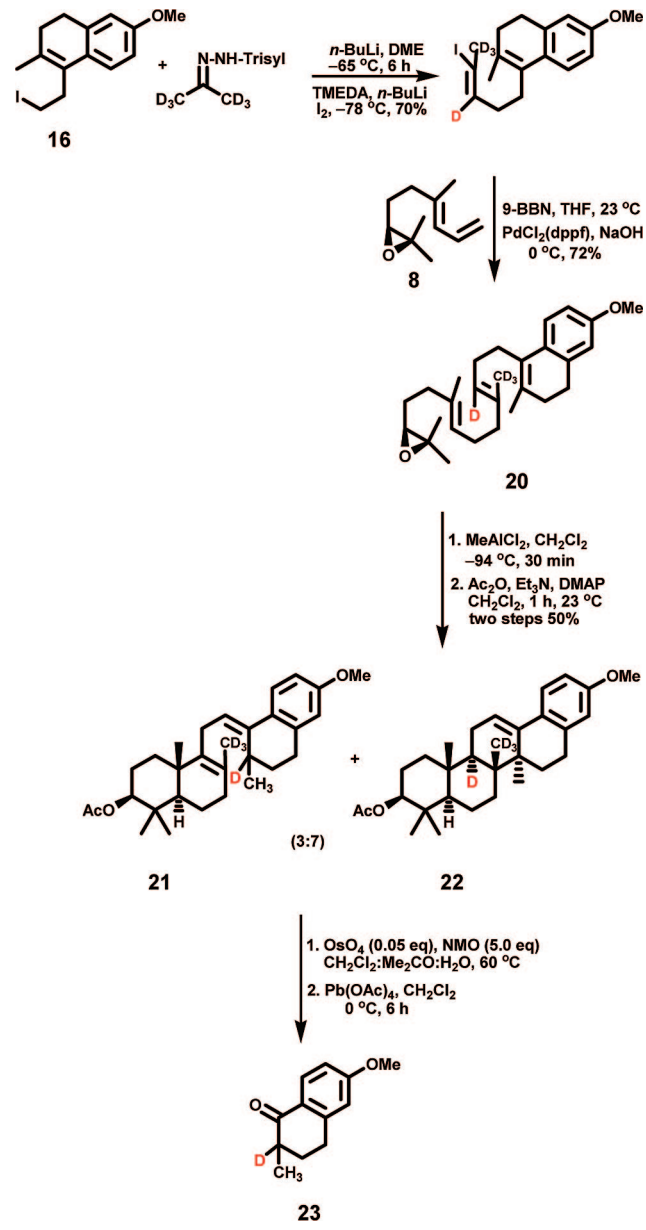


Scheme 4



in more detail with very interesting results. Control experiments confirmed that tetracycle **11** is not converted to pentacycle **2** under the conditions shown in Scheme 2 ($MeAlCl_2$, CH_2Cl_2, −94 °C) or even at much longer reaction times. Nor was **2** transformed into **11** under these conditions. Therefore, it is clear that **2** and **11** are formed independently by a split pathway from the common precursor, cation **18** (Scheme 4). The branch leading from **18** to **11**, as shown in Scheme 4, would appear to involve a highly unusual acyclic, 1,5-migration of a *proton* from the C(9) (*β*- to the cationic center at C(8) to C(13)) to form the benzylic cation **19** and the further deprotonation of **19**, as shown. This is a rare (and possibly unprecedented) example of such an intramolecular rearrangement. It is clear that $\Delta H^{\ddagger}$ for the intramolecular proton transfer to the vinyl arene subunit must be quite small, if the pathway shown in Scheme 4 is correct, since $\Delta H^{\ddagger}$ for

Scheme 5

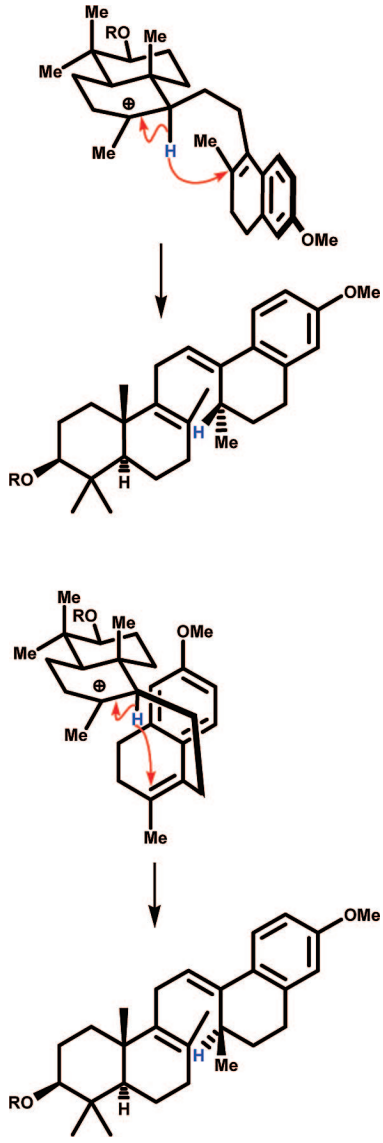


the addition of a *t*-butyl carbocation to isobutylene in CH_2Cl_2 has been calculated to be only ca. 3−5 kcal/mol.[15]

We have subjected the hypothetical pathway **18** → **19** → **11** to an experimental test because it is so poorly precedented. Specifically, the tetradeuterated epoxide **20** (corresponding to unlabeled **10**) was synthesized as shown in Scheme 5. Cyclization of **20** in CH_2Cl_2 with $MeAlCl_2$ as catalyst at −94 °C provided the tetradeuterated products **21** and **22** (ratio of 3:7, as expected). Oxidation of the mixture of **21** and **22** provided the tetralone **23** and unchanged **22** (Scheme 5). Analysis of **23** by ^{1}H NMR and mass spectroscopy showed it to be the α-monodeuterated ketone **23**, which moreover was *racemic*, as shown by HPLC analysis using a Chiralcel technologies OD-H column (hexanes/*i*-PrOH 99.5:0.5, flow rate 1.0 mL/min; retention times: 20.0, 22.1 min[16]).

(15) Jenson, C.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 10846–10856.
(16) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349.

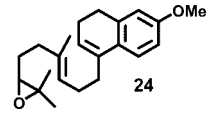
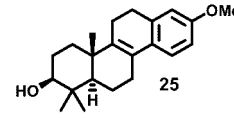
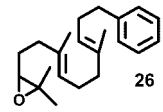
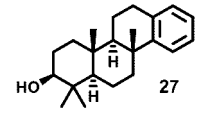
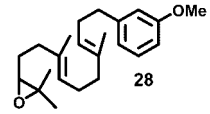
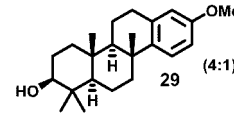
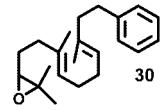
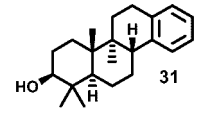
Scheme 6



The formation of racemic tetralone shows that the tetracycles **11** and **21** are actually a 1:1 mixture of C(14) diastereomers formed by the two simultaneous diastereomeric rearrangement pathways shown in Scheme 6.

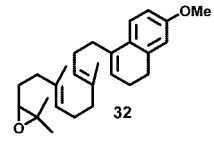
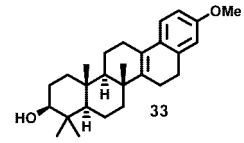
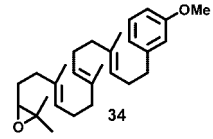
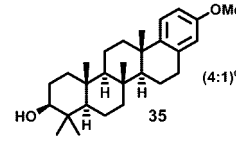
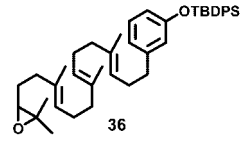
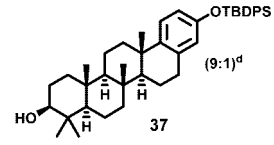
The two synthetic approaches to **1** and **2** that are described above confirm the utility and power of the newer synthetic methods that were employed. In particular, the efficient construction of chiral epoxy polyolefinic substrates by stereoselective multicomponent coupling reactions, together with the use of epoxide-initiated cation−olefin polyannulation can lead to especially short and effective syntheses. The value of this tactical combination could be increased to an even higher level if the efficiency of the cationic polyannulation could be increased. This need represents one of the outstanding challenges to present day synthetic science. Overcoming this obstacle probably requires the invention of a methodology that folds the polyolefinic substrate into a conformation that is ideal for polyannulation to the required stereoisomer using some type of control element. Such a preorganization would surely lead to a much less negative $\Delta S^{\ddagger}$ for the cyclization and a considerably higher yield. The enhancement would be especially significant for cyclizations in which quaternary stereocenters and sterically congested products are being formed.

Table 1. $MeAlCl_2$−Catalyzed Epoxide-Initiated Cation−Olefin Cyclization Reactions

Entry	Substrate	Product	Yield (%)[a,b]
1	 24	 25	72[c]
2	 26	 27	60
3	 28	 29 (4:1)[d]	58
4	 30	 31	52

[a] All reactions were carried out at −94 °C and 3.0 equiv of $MeAlCl_2$ in CH_2Cl_2. [b] Isolated yields of products that were fully characterized by NMR, IR, and MS. [c] A mixture of two double bond position isomers (1:1) resulted, which was converted to pure **25** by treatment with CH_3SO_3H in CH_2Cl_2. [d] Reaction afforded a mixture of para-/ortho-substituted products.

Table 2. $MeAlCl_2$−Catalyzed Epoxide-Initiated Cation−Olefin Cyclization Reactions

Entry	Substrate	Product	Yield (%)[a,b]
5	 32	 33	55[c]
6	 34	 35 (4:1)[d]	38
7	 36	 37 (9:1)[d]	48

[a] All reactions were carried out at −94 °C and 3.0 equiv of $MeAlCl_2$ in CH_2Cl_2. [b] Isolated yields of products that were fully characterized by NMR, IR, and MS. [c] A mixture of two double bond position isomers (1:1) resulted, which was converted to pure **33** by treatment with CH_3SO_3H in CH_2Cl_2. [d] Reaction afforded a mixture of para-/ortho-substituted products.

We have also applied the present methodology to the synthesis of a number of other tetra- and pentacyclic products. We summarize some of the results in Table 1 (tetracyclic products) and Table 2 (pentacyclic products), which display various polyolefinic substrates and the products obtained from them by $MeAlCl_2$-catalyzed, epoxide-initiated cation−olefin cyclization in CH_2Cl_2 as solvent. The details of these cyclizations and routes for the synthesis of the various substrates can be found in the Supporting Information.

In conclusion, this research has demonstrated the synthetic efficacy of multicomponent chain-assembly using sulfonylhydrazone or acyl silane chemistry and the overall synthetic power of the tactical combination of this methodology with cationic polyannulation reactions. We have also described the occurrence of a remarkable 1,5-proton shift reaction which is so facile that it competes with carbocation−olefin addition.

Supporting Information Available: Experimental procedures and characterization data for all reactions and products, including copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA802730A