JOC*Article*

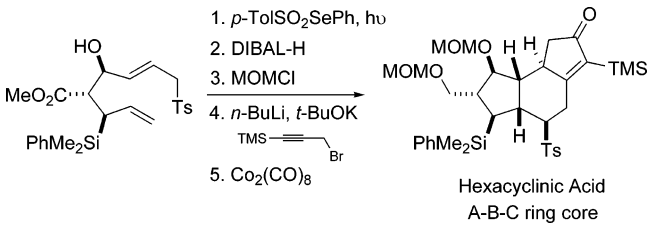
Free-Radical-5-*exo*-Trig Cyclization of Chiral 3-Silylhepta-1,6-dienes: Concise Approach to the A−B−C Ring Core of Hexacyclinic Acid†

Philippe James,‡ François-Xavier Felpin,‡ Yannick Landais,*,‡ and Kurt Schenk§

Université Bordeaux-I, Laboratoire de Chimie Organique et Organométallique, 351, Cours de la Libération, 33405 Talence Cedex, France and Université de Lausanne, Institut de Cristallographie, BPS Dorigny, CH-1015 Lausanne, Suisse

y.landais@lcoo.u-bordeaux1.fr

Received May 27, 2005

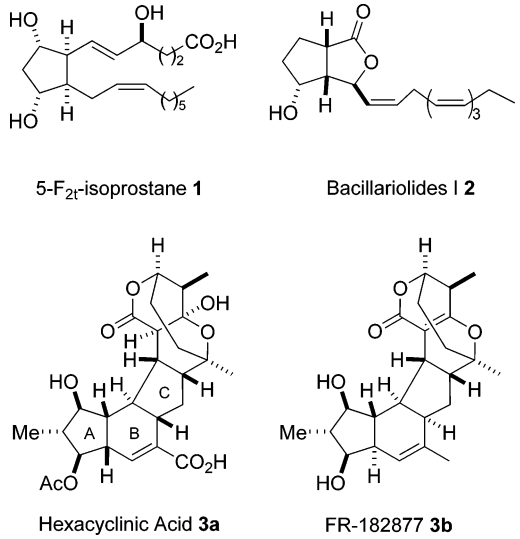


Free-radical-mediated 5-*exo*-trig cyclization of hepta-1,6-dienes **6a**−**c** incorporating an allylsilane moiety was shown to provide at low temperature exclusively the trans-cis cyclopentanes **7a**−**c** in good yield. In contrast, the same reaction with the alkyl analogue **9a** led to the formation of all four possible stereoisomers. Interestingly, extension of this sequence of radical processes to alkoxy analogues **12**−**14** provided the complementary cis-cis stereoisomers with modest to excellent stereoselectivity. It is noteworthy that under such conditions allylsilanes were found to be much more reactive than their alkyl and alkoxy analogues. Beckwith−Houk-type models were proposed that rationalize the stereochemical course of these 5-*exo*-trig cyclizations. Finally, an illustration of the value of this methodology was proposed with the synthesis of the A−B−C tricyclic unit of polyketide hexacyclinic acid **3a**.

Introduction

Five-membered ring systems are common structural units in natural products (i.e., **1**−**3**, Scheme 1) and are ubiquitous in Nature.[1] Important efforts have thus been devoted to construct a polysubstituted five-membered-ring core in a diastereo- and enantiocontrolled manner.[2] The cyclopentane skeleton may be embedded in a complex polycyclic system as in **3a,b** or may represent the key structural element as in **1** or **2**. 5-*exo*-Trig cyclizations are known to be efficient processes under anionic[3] and

SCHEME 1. Natural Products Containing Cyclopentanes



† Taken as a part of the Ph.D. thesis of P.J., University Bordeaux-I (Oct 2004).

‡ Université Bordeaux-I.

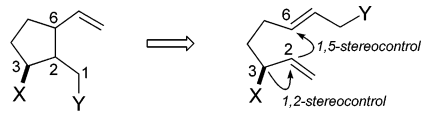
§ Université de Lausanne.

(1) (a) **1** is produced in vivo in Humans, see: Taber, D. F.; Xu, M.; Hartnett, J. C. J. *J. Am. Chem. Soc.* **2002**, *124*, 13121−13126 and references therein. (b) **2** was isolated from marine diatom, see: Wang, R.; Shimizu, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 413−413. (c) **3a** was isolated from *Streptomyces cellulosae* subsp, see: Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258−3261. (d) **3b** was isolated from *Streptomyces* sp. *No9885*, see: Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123−130.

(2) (a) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257−1280. (b) Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans 1* **2000**, 477−501. (c) Hassner, A.; Ghera, E.; Yechezkel, T.; Kleiman, V.; Balasubramanian, T.; Ostercamp, D. *Pure Appl. Chem.* **2000**, *72*, 1671−1683. (d) Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385−1489.

10.1021/jo051062g CCC: $30.25
Published on Web 09/02/2005

SCHEME 2. 5-*exo*-Trig Cyclization of Chiral 1,6-Heptadienes



4, X = SiR_3, OR, alkyl
Y = *p*-$TolSO_2$

5

free-radical conditions[4] and thus constitute methods of choice to elaborate five-membered ring skeletons in a limited number of steps with generally high selectivity and yield. Among the cyclization processes, radical-mediated cyclizations[4] have attracted a great deal of attention and hold a special place. The kinetics of these transformations have been studied in depth, and rate constants are available for most systems possessing a wide range of atoms within the ring (C, O, N, Si,...).[5]

We recently started a study on the elaboration of polysubstituted five-membered ring systems **4** relying on the radical cyclization of 1,6-dienes **5** containing an allylsilane moiety (Scheme 2).[6] Our strategy was based on utilization of a radical cascade involving addition of a tosyl group, 5-*exo*-trig cyclization followed, by β-fragmentation. This approach is well known to lead, with generally high efficiency and under mild conditions, to the corresponding five-membered ring (i.e., **4**) having two new contiguous stereogenic centers.[7] Several examples of this transformation have been reported which emphasize the problem of stereocontrol arising in this process.[8] While an excellent level of 1,2-stereocontrol is generally granted with systems having an allylic substituent (at C3), generally poor to modest 1,5-stereocontrol is observed in those cases. Studies in our group and others[9] have convincingly demonstrated that in various processes involving chiral organosilicon compounds with a silicon group on a stereogenic center a high level of stereocontrol could be attained. The presence of a bulky silicon group within a chain restricts the number of reactive conformations at the transition state, leading to a high level of transfer of chiral information. It was thus anticipated that the presence of a silicon group in the allylic position in systems such as **5** would allow, during step **5** → **4** (Scheme 2), control of the relative configuration between stereogenic centers at C2 and C3 (1,2-stereocontrol) but also between C2 and C6 (1,5-stereocontrol), taking advantage of both the steric and electronic effects of the silicon group. Our study was effectively based on the assumption that the steric hindrance of SiR_3 would lead to a decrease in the number of reactive conformations at the cyclization transition state[9a,d] and that the partial positive charge developing at C2 upon cyclization could be stabilized by the β-silicon group,[10,11] thus reinforcing the inherent steric effect of this group. Precedent in the laboratory on radical functionalization of chiral allylsilanes supported such a hypothesis.[12]

We thus provide here a full account of our studies on free-radical-mediated 5-*exo*-trig cyclization of dienes of type **5** having an allylsilane moiety. The study was also extended to models having various substituents at the allylic position (X = alkyl, OR) with the aim of presenting a consistent picture of the effects controlling the stereochemistry of this 5-*exo*-trig process. Finally, an illustration of the utility of such an approach for the stereoselective construction of cyclopentanoids is provided with a concise synthesis of a precursor of the ABC ring core of hexacyclinic acid **3a**, the total synthesis of which has not yet been disclosed.

Results and Discussion

5-*exo*-Trig Cyclizations of Allylsilane Precursors. Preliminary investigations were carried out using two distinct 1,6-diene models **6a**[6] and **6b,c**[6] having, respectively, one and two stereogenic centers. We started our studies by performing the radical 5-*exo*-trig cyclizations under thermal conditions using AIBN as an initiator and a catalytic amount of *p*-$TolSO_2SePh$. Reaction of **6a** led to the desired cyclopentanes **7a** and **8a** in reasonable yield with modest stereocontrol (Entry 1, Table 1). A combination of 1D and 2D NMR studies unambiguously established that the major isomer **7a** possessed the trans-cis relative configuration, while the minor isomer **8a** possessed the trans-trans configuration. 1,2-Stereocontrol was thus excellent, in good agreement with previous reports from the literature,[8] but 1,5-stereocontrol remained modest. To our delight, much better results were obtained by performing the reaction at room temperature

(3) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Baldwin, J. E., Williams, R. M., Eds.; Tetrahedron Organic Chemistry Series; Pergamon: Amsterdam, 2002; Vol. 23, Chapter 7, pp 274−335.

(4) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073−3100. (b) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Heterocycles* **2004**, *63*, 1903−1958 and references therein.

(5) (a) Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157−173. (b) Wilt, J. *Tetrahedron* **1985**, *41*, 3979−4000. (c) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281−287.

(6) James, P.; Landais, Y. *Org. Lett.* **2004**, *6*, 325−328.

(7) (a) Bertrand, M.-P.; De Riggi, I.; Lesueur, C.; Gastaldi, S.; Nouguier, R.; Jaime, C.; Virgili, A. *J. Org. Chem.* **1995**, *60*, 6040−6045. (b) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2346−2352. (c) Harvey, I. W.; Philips, E. D.; Whitham, G. H. *Tetrahedron* **1997**, *53*, 6493−6508. (d) Harvey, I. W.; Whitham, G. H. *J. Chem. Soc., Perkin Trans 1* **1993**, 185−190. (e) Harvey, I. W.; Whitham, G. H. *J. Chem. Soc., Perkin Trans 1* **1993**, 191−196. (f) Smith, T. A. K.; Whitham, G. H. *J. Chem. Soc., Perkin Trans 1* **1989**, 319−325. (g) Chuang, C.-P. *Tetrahedron* **1991**, *47*, 5425−5436.

(8) (a) Bertrand, M.-P.; Gastaldi, S.; Nouguier, R. *Tetrahedron Lett.* **1996**, *37*, 1229−1232. (b) Bertrand, M.-P.; Gastaldi, S.; Nouguier, R. *Tetrahedron* **1998**, *54*, 12829−12840. (c) Nouguier, R.; Gastaldi, S.; Stien, D.; Bertrand, M.-P.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3371−3374. (d) Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed. Engl.* **2003**, *47*, 4043−4046.

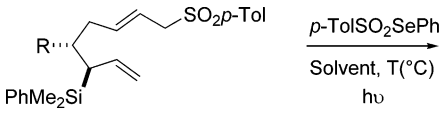
(9) (a) Fleming, I.; Dunoguès, R.; Smithers, R. *Org. React.* **1989**, *37*, 57−575. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192. (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. (d) Fleming, I. *J. Chem. Soc., Perkin Trans 1* **1992**, 3363−3369. (e) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173−3199.

(10) For reviews on the β-silicon effect, see: (a) Panek, J. S. Silicon Stabilization. In *Comprehensive Organic Chemistry*; Trost, B., Fleming, I., Eds.; 1989; Vol. 1, 579−627. (b) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677−2689. (c) Jarvie, A. W. P. *Organomet. Chem. Rev., Sect. A* **1970**, *6*, 153−207. (d) White, J. M. *Aust. J. Chem.* **1995**, *48*, 1227−1251.

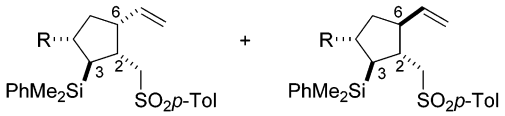
(11) For the stabilization of β-carboradicals by a silicon group, see: (a) Kawamura, T.; Kochi, J. K. *J. Am. Chem.* Soc. **1972**, *94*, 648−650. (b) Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6715−6720. (c) Jackson, R. A.; Ingold, K. U.; Griller, D.; Nazran, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 208−211. (d) Auner, N.; Walsh, R.; Westrup, J. *J. Chem. Soc., Chem. Commun.* **1986**, 207−207.

(12) (a) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2002**, *4*, 4257−4260. (b) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773−5777. (c) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587−2590.

TABLE 1. Sulfonyl Radical-Mediated 5-*exo*-Trig Cyclization of Dienes 6a−c



6a, R = H
6b, R = CO_2Me
6c, R = CH_2OH



7a, R = H
7b, R = CO_2Me
7c, R = CH_2OH

8a, R = H
8b, R = CO_2Me
8c, R = CH_2OH

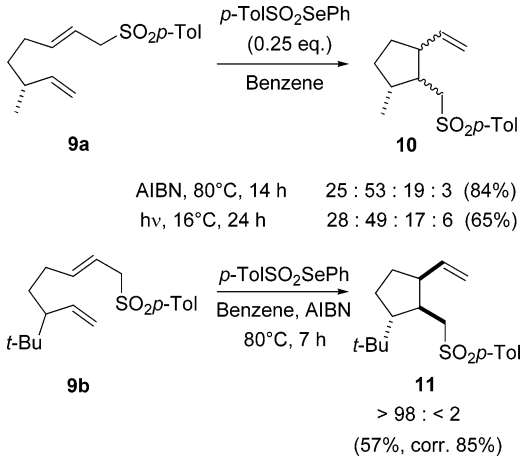
entry	diene	solvent	cat.	*T* (°C)	time (h)	d.r.[a]	yield (%)[b]
1	**6a**	C_6H_6	0.15	80[c]	10	86:14	69
2	**6a**	C_6H_6	0.15	16	4	96:4	83
3	**6a**	CCl_4	0.15	−15	2.5	98:2	85
4	**6a**	$CHCl_3$	0.15	−50	3	>99:<1	84
5	**6a**	$CHCl_3$	0.25	−50	0.5	>99:<1	85
6	**6b**	C_6H_6	0.15	16	8	81:19	85
7	**6b**	$CHCl_3$	0.15	−50	3	95:5	72
8	**6b**	$CHCl_3$	0.25	−50	0.5	95:5	79
9	**6b**	CH_2Cl_2	0.5	−78	3.5	>99:<1	56
10	**6c**	$CHCl_3$	0.25	−50	0.5	>99:<1	61

[a] Estimated from ^1H NMR and GC analysis of the crude reaction mixture. [b] Isolated yields after purification through chromatography. [c] AIBN was used as an initiator.

under irradiation (sun lamp), where cyclopentane **7a** was obtained in 92% de in an improved 83% yield (entry 2). Lowering the temperature to −15 °C and then −50 °C finally led to complete stereocontrol with **7a** obtained as a unique diastereomer (GC) (entries 3 and 4). Increasing the amount of catalyst from 0.15 to 0.25 equiv also allowed the reaction to be carried out in only 0.5 h at −50 °C with the same yield (entry 5). It is worth noting that the stereochemistry of the starting sulfone **6a** had no effect on the stereocontrol as the reaction carried out on a 10:1 *E*/*Z* mixture led to a 98:2 **7a**/**8a** ratio at −50 °C (with 0.25 equiv of *p*-TolSO_2SePh in $CHCl_3$, 0.5 h). These conditions were then applied to allylsilane **6b**, which afforded the corresponding cyclopentanes **7b**/**8b** with a high level of stereocontrol. At −50 °C (entries 7 and 8) the stereocontrol was slightly lower than that observed for analogue **6a**. Complete stereocontrol, albeit with moderate yield, was however observed at −78 °C using 0.5 equiv of catalyst (entry 9). The relative configuration of **7b** was finally secured through X-ray crystallographic structure determination, thus supporting the configuration of **7a** established through NMR studies in advance. Similarly, cyclization of diene **6c** under optimized conditions led to cyclopentane **7c** as a unique stereoisomer (entry 10).

5-*exo*-Trig Cyclizations of Dienes Bearing various Substituents in the Allylic Position (C3). Intrigued by these results, we then examined the 5-*exo*-trig cyclization of a series of analogues of **6a−c** having various substituents in the allylic position. Alkyl substituents such as methyl and *tert*-butyl groups were selected to study the conformational preferences induced by small and large alkyl groups in allylic positions and allow comparisons with the silicon group.[13] Oxygenated substituents (OH, OR, and OCOR groups) were also studied as it was anticipated that an alkoxy group (or an ester) would introduce opposite electronic effects to that of a silicon group.[14] It was thus envisioned that this series of experiments would provide some insight into the effects (steric or/and electronic) governing the stereochemistry of these 5-*exo*-trig cyclizations.

SCHEME 3. Sulfonyl Radical-Mediated 5-*exo*-Trig Cyclization of Dienes 9a,b



Precursor **9a** bearing an allylic methyl substituent was thus prepared in six steps from (*R*)-(−)-citronellene.[6] **9b** possessing a *t*-Bu group in allylic position was also prepared in four steps from 4-*tert*-butylhex-5-enal (itself prepared in five steps from 4-*tert*-butylcyclohexanone).[15] Precursors **9a,b** were then treated as above for allylsilanes **6a−c** using 0.25 equiv of *p*-TolSO_2SePh in benzene or $CHCl_3$ at various temperatures (Scheme 3). **9a** thus afforded the expected cyclopentane **10** but as an inseparable mixture of four diastereomers whatever the temperature. When the reaction was carried out at −78 °C, only trace amounts of cyclopentanes were observed after 8 h, showing the lack of reactivity of alkyl precursors as compared to their silylated analogues.[16] Similarly, precursor **9b** exhibited no reactivity at room temperature, and cyclization product **11** was only formed after 7 h at 80 °C with a modest conversion (57%) but as a single diastereomer having trans-cis stereochemistry, as shown by X-ray crystallographic analysis (Supporting Information). Finally, under similar conditions the ramified isomer of **9b** also led to cyclopentane **11** with only 15% conversion.

Precursor **12** having an allylic alcohol moiety was prepared from hexa-1,5-diene.[6,17] Tuning the electronic

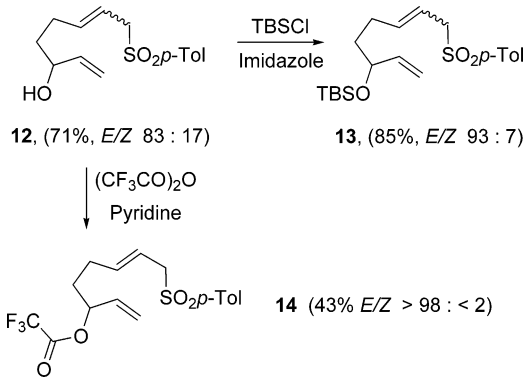
(13) An *A* value of 4.7−4.9 has been estimated for a *t*-Bu group as compared to 2.5 for a silicon group, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 11, pp 696−697.

(14) (a) Fleming, I.; Sarkar, A. K.; Doyle, M. J.; Raithby, P. R. *J. Chem. Soc., Perkin Trans 1* **1989**, 2023−2030. (b) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257−3262. (c) Landais, Y.; Planchenault, D.; Weber, V. *Tetrahedron Lett.* **1995**, *36*, 2987−2990. (d) Andrey, O.; Landais, Y. *Tetrahedron Lett.* **1993**, *34*, 8435−8438.

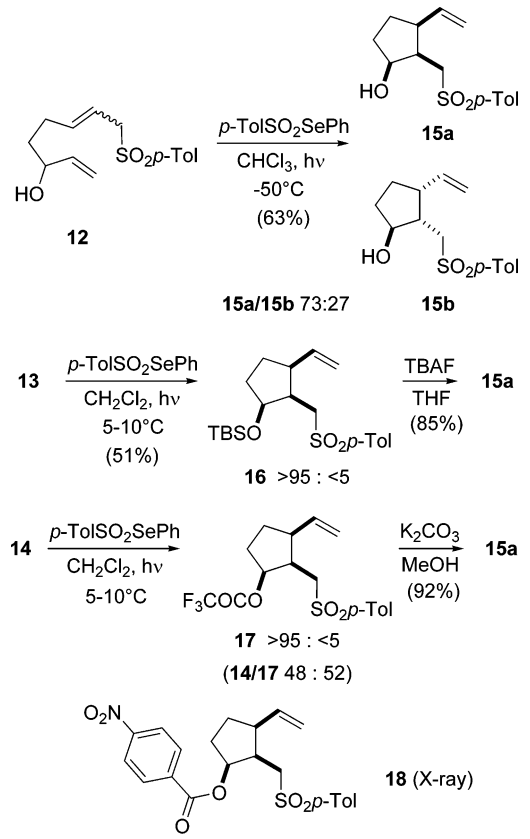
(15) Inoue, H.; Murata, S.; Suzuki, T. *Liebigs Ann. Chem.* **1994**, 901−909.

(16) Cyclization of the achiral analogue of **9a**, lacking the allylic Me group, provided a 3:1 cis/trans ratio at best, in good agreement with earlier reports.[7]

SCHEME 4. Preparation of Oxygenated Precursors 12−14



SCHEME 5. Sulfonyl Radical-Mediated 5-*exo*-Trig Cyclization of Dienes 12−14



and steric properties of the allylic alkoxy group was also made possible through protection of the alcohol function of **12** with two different protective groups as in silyl ether **13** and trifluoroacetate **14** (Scheme 4).

Dienes **12**−**14** were then treated as above with *p*-TolSO$_2$SePh in CHCl$_3$ or CH$_2$Cl$_2$ to provide the desired cyclopentanes with modest to excellent levels of stereocontrol (Scheme 5). Alcohol **12** was thus shown to provide a 73:27 mixture of two stereoisomers **15a/15b**, with the major one having the cis-cis relative configuration. Both stereoisomers were separated by chromatography, and their configurations were determined using NOESY experiments. Confirmation of the stereochemistry of the major isomer **15a** was obtained through X-ray structure determination of the nitrobenzoate **18**. The minor isomer **15b** was shown to possess the trans-cis relative configuration (NOESY), similar to that of silylated analogues **7a**−**c** (vide supra). The study was next extended to silylated analogue **13**, which at 5−10 °C with 0.45 equiv of *p*-TolSO$_2$SePh in CH$_2$Cl$_2$ led to cyclopentane **16** in 51% isolated yield as a unique stereoisomer. The reactivity of **13** was found to be much lower than that of the parent alcohol, with a 31:52:17 **13/16/15a** ratio (^{1}H NMR) observed after 8 h of irradiation. Desilylation of **16** using TBAF led to alcohol **15a** having cis-cis stereochemistry, indicating that cyclopentane **13** had the same cis-cis relative configuration.[18] Reaction of trifluoroacetate **14** afforded cyclopentane **17** as the only observable isomer, albeit in modest yield due to low conversion. Similar to the silylated precursor **13**, trifluoroacetate **14** was poorly reactive at −50 °C, producing only trace amounts of cyclopentane **17** after several hours. At −25 °C and irradiation for 7 h a 64:33 **14/17** ratio was estimated by ^{1}H NMR. Finally, the best levels of conversion with a 48:52 **14/17** ratio were obtained at 5−10 °C with 0.45 equiv of *p*-TolSO$_2$SePh in CH$_2$Cl$_2$. Under these conditions a clean reaction occurred as shown by the ^{1}H NMR spectrum of the crude reaction mixture, where only the starting material and the desired cyclopentane **17** were obtained in quantitative yield. Attempts to separate cyclopentane **17** from the starting material were plagued by its sensitivity to silica gel. Nevertheless, diastereoisomerically pure **17** could be isolated, albeit in a 17% yield, after careful chromatography onto silica gel. Removal of the trifluoroacetate group under basic conditions led to alcohol **15a** with a cis-cis relative configuration, demonstrating that sulfonyl-mediated 5-*exo*-trig cyclization of alcohol **12** and its trifluoroacetate analogue **14** proceeded with the same stereochemistry and complete 1,2- and 1,5-stereocontrol for the latter. The results obtained in the alkoxy series are appealing since the stereochemistry observed in this case is complementary to that of the silicon series. Considering that a C−Si bond can be oxidized into the corresponding C−OH bond with *retention of configuration*,[19] we thus have complementary access to stereochemically pure trans-trans and trans-cis trisubstituted cyclopentanols.

Discussion−Transition-State Models

The concomitant 1,2- and 1,5-stereocontrol observed during 5-*exo*-trig cyclizations of allylsilanes **6a**−**c** into cyclopentanes **7a**−**c** was rationalized, assuming a chair-like transition state **A**, with the bulky silicon group in a pseudoequatorial position (Figure 1). Such a conformation at the transition state is closely related to that proposed for simpler systems by Beckwith and Schiesser[20a−c] and later by Houk et al.[20d] The minor isomer would be formed through a boatlike transition state **B** with a silicon group again in a pseudoequatorial position. Such a boat con-

(17) (a) Baylon, C.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354−3360. (b) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 30, 5449−5452.

(18) Roland, A.; Durand, T.; Egron, D.; Vidal, J.-P.; Rossi, J.-C. *J. Chem. Soc., Perkin Trans 1* **2000**, 245−251.

(19) (a) Fleming, I. *Chemtracts, Org. Chem.* **1996**, *9*, 1−64. (b) Tamao, K. *Adv. Silicon Chem.* **1996**, *3*, 1−62. (c) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.

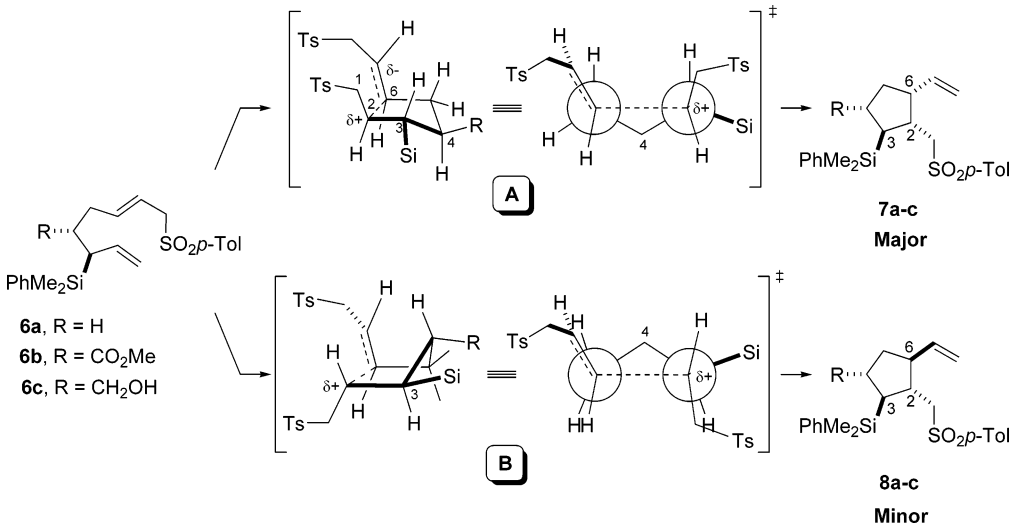


FIGURE 1. Transition-state models for 5-*exo*-trig cyclizations of precursors **6a**−**c**.

formation does not suffer here from the flagpole interactions observed in cyclohexane and can thus be invoked.[20d] Such a conformation would be more favorable than a chairlike conformation in which the silicon group would be forced into a pseudoaxial arrangement, generating important 1,3-diaxial interactions. **TS**−**B** however experiences more important torsional strain, explaining its higher energy as compared to **TS-A**. Interestingly, the Newman representation of **TS-A** and **TS-B** shows that the C−Si bond is nearly aligned with the incipient C−C bond and thus stabilizes the developing positive charge at C2. Such an effect, reminiscent of the β-silicon effect,[10] may explain in part the unusual reactivity of allylsilanes in this radical cascade process (i.e., stabilization of the transition state). The matched polarity between electron-rich allylsilanes[21] and electrophilic tosyl radical may also contribute to the high observable rate, as compared with the alkyl and alkoxy analogues. It has effectively been shown that electrophilic radical species such as $MeSO_2^{\cdot}$ or $CCl_3^{\cdot}$ add faster to allylsilanes than to the corresponding olefins lacking a silicon group.[22] The origin of the high 1,2- and 1,5-stereocontrol observed during cyclization of allylsilanes (and allylic *t*-Bu precursor **9b**) is more difficult to rationalize. Complete 1,2- and 1,5-stereocontrol observed during cyclization of *t*-Bu precursor **9b** at 80 °C tends to support the steric origin of the stereoselectivity in these systems. It is noteworthy that **11** was obtained as a unique stereoisomer at 80 °C, while at the same temperature silylated analogues **7a/8a** were formed in a 86:14 ratio, indicating that the *t*-Bu group is a more efficient "chiral inducer" that a $PhMe_2Si$ group, in line with the respective *A* value of these groups.[13] Cyclopentane **11** is thus likely to be formed through a chairlike transition state such as **A**, efficiently locked by the *t*-Bu group (Figure 1). It is known in radical hex-5-enyl cyclizations that conformationally more rigid systems lead to higher stereocontrol.[23] The bulky silicon and *t*-Bu groups on the heptadienyl chain probably limit the number of conformations available for cyclization and efficiently lock these conformations. In contrast, substitution of the silicon group with a smaller methyl substituent (i.e., as in precursor **9a**) leads to a conformationally more flexible system, where nonchairlike conformations (i.e., **TS-B**) are also highly populated, leading to a mixture of 2,6-cis and 2,6-trans diastereomeric products. Additional electronic effects may also be invoked and cannot be ruled out. In his seminal papers[20a,b,24] Beckwith rationalized formation of the major 2,6-cis stereoisomer (1,5-stereocontrol), considering that these 5-*exo*-trig radical cyclizations likely proceed through a dipolar transition state, involving an electrostatic interaction between the "negatively charged ($\delta-$)" olefinic moiety and the positively charged radical center C2 (δ^+) (Figure 1).[24b,c] Stabilization of this partial positive charge by the SiR_3 group, through hyperconjugation, might reinforce this electrostatic interaction in our case. Therefore, both steric and electronic effects would cooperate to favor the formation of the trans-cis compounds.[25]

The contrasting formation of the major cis-cis stereoisomer **15a** in the alkoxy series may arise through transition state **C** (Figure 2) in which the alkoxy group at C3 prefers the pseudoaxial position for electronic reasons.[26] As shown in the Newman representation, a

(20) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373−376. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941. (c) Beckwith, A. L. J.; Zimmermann, J. *J. Org. Chem.* **1991**, *56*, 5791−5796. (d) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−974.

(21) Ground-state interactions between the σ_{C-Si} bond and the olefin raise the HOMO of the allylsilane, making it more reactive towards electrophiles, see: (a) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650−663. (b) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7396−7398.

(22) (a) Sakurai, H.; Hosomi, A.; Kumada, M. *J. Org. Chem.* **1969**, *34*, 1764−1768. (b) Gozdz, A. S.; Maslak, P. *J. Org. Chem.* **1991**, *56*, 2179−2189. (c) Chatgilialoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 6387−6390. (d) Jarvie, A. W. P.; Rowley, R. J. *J. Chem. Soc., B* **1971**, 2439−2442.

(23) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139−145 and references therein.

(24) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073−3100. (b) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613−1614. (c) Shono, T.; Nishigushi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545−550.

(25) Tripp, J. C.; Schiesser, C. H.; Curran, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 5518−5527.

(26) (a) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, G.; Jung, J.; Rancourt, J. *J. Org. Chem.* **1994**, *59*, 1166−1178. (b) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912−4914.

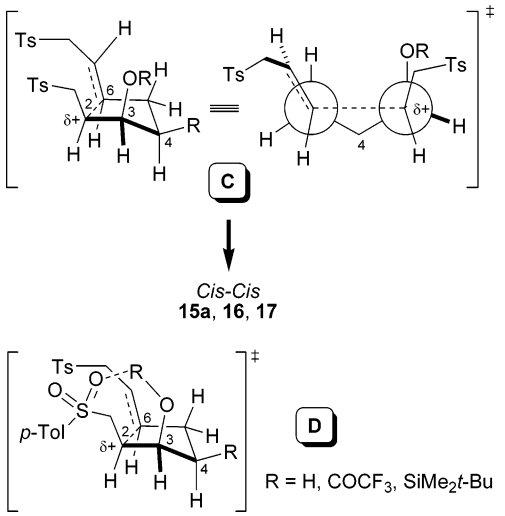


FIGURE 2. Transition-state models for 5-*exo*-trig cyclizations of precursors **12**−**14**.

pseudoaxial OR group would be orthogonal to the electron-deficient forming C−C bond and to the developing partial positive charge at C2. This charge would thus be better stabilized by the nearly aligned C3−H bond as a σ_{C-H} bond is a better electron donor than a σ_{C-O} bond. The occurrence of such an effect is further supported by the complete stereocontrol, albeit with modest conversion, observed with precursor **14** in which the strong electron-withdrawing CF_3CO_2 group at C3 should reinforce this electronic effect. The incomplete conversion during cyclization of diene **14** may be ascribed to the low reactivity of the reacting olefin which is strongly deactivated by the trifluoroacetate group, indicating again the importance of polar effects in addition of electrophilic sulfonyl groups onto olefins.[22b] Similar selectivities were obtained with precursor **13** having a sterically hindered TBDMS group. These results were at first glance relatively surprising as it was expected that a bulky TBDMS group would behave very much like a $PhMe_2Si$ group to lead predominantly to the trans-cis isomer.[18] It is however plausible that the silicon group on the oxygen is pointing away and would thus be quite remote, thus having little influence on the stereocontrol. An alternative model **D** may also be proposed, invoking in the case of precursor **12**, hydrogen bonding between the alcohol function and the closest sulfonyl group (Figure 2). Such an interaction would thus maintain the OH group in a pseudoaxial position. Although such an interaction seems to be disproved by the better stereocontrol observed with precursors **13** and **14**, in which hydrogen bonding is precluded, interactions between the sulfonyl group and the trifluoroacetate carbonyl group (R = $COCF_3$) in **14** or the TBDMS group (R = $SiMe_2t$-Bu) in **13** cannot be ruled out. The electronic effect discussed above and the *p*-$TolSO_2$ ↔ R group interaction may also reinforce one another and contribute to the high level of 1,2- and 1,5-stereocontrol observed with models **13** and **14**. Finally, the minor isomer **15b**, only observed upon cyclization of the alcohol precursor **12**, is likely to be formed through a transition state close to **TS-A** (Figure 1) with the OH group in a pseudoequatorial position. Such a conformation would not be favored as the OH group electronic effect and the hydrogen-bonding interaction discussed above could not operate.

Approach toward the A−B−C Ring Core of Hexacyclinic Acid. Having demonstrated that high 1,2- and 1,5-stereocontrol could be attained during radical 5-*exo*-trig cyclizations of the hepta-1,5-dienyl system having an allylsilane moiety, we then attempted to illustrate the utility of such a methodology in the preparation of the A−B−C ring core of hexacyclinic acid **3a**, a polyketide recently isolated from *Streptomyces cellulosae* subsp. griserubiginosus (strain S1013).[1c] This polycyclic system is structurally very close and probably biosynthetically related to (−)-FR-182877 **3b**, isolated from *Streptomyces* sp. No. 9885,[1d] which, however, exhibits much higher cytotoxicity than **3a**. While (−)-FR-182877 **3b** has recently been synthesized using biomimetic strategies, involving as key steps aldol and transannular Diels−Alder processes,[27] hexacyclinic acid **3a** has not yet succumbed to total synthesis. However, recent studies have shown that the A−B−C ring of **3a** may also be assembled through a Diels−Alder approach,[28a] while construction of the D−E−F ring was performed through a transannular iodocyclization of a nine-membered ring β-ketoester.[28b,c] Our approach to A−B−C ring precursor **I** follows a different pathway in which the tricyclic skeleton would be constructed in two steps, i.e., a 5-*exo*-trig radical cyclization as described above and a Pauson−Khand reaction[29] (Scheme 6). The alcohol function at C8 (following hexacyclinic acid numbering[1c]) could then be generated at a suitable time through Tamao−Kumada−Fleming oxidation[19] of the C−Si bond and the methyl group at C7 generated from the corresponding hydroxymethyl moiety. It was envisioned that the tricyclic skeleton of **I** could be easily assembled through Pauson−Khand cyclization of a suitable enyne **II**, itself obtained through alkylation of the sulfone **III**.[30] Although many examples of such intramolecular Pauson−Khand processes have been reported before,[29] it was however not possible at this point to make certain the control of the stereochemistry at C4. Sulfone **III** would be obtained through the sulfonyl addition−5-*exo*-trig-β-elimination cascade studied above with the concomitant control of the relative configuration at C5, C8, and C9. Cyclization of precursor **IV** would in turn be formed using an aldol process between a β-silyl ester such as **VI** and aldehyde **V**. Previous studies indicate that the relative configura-

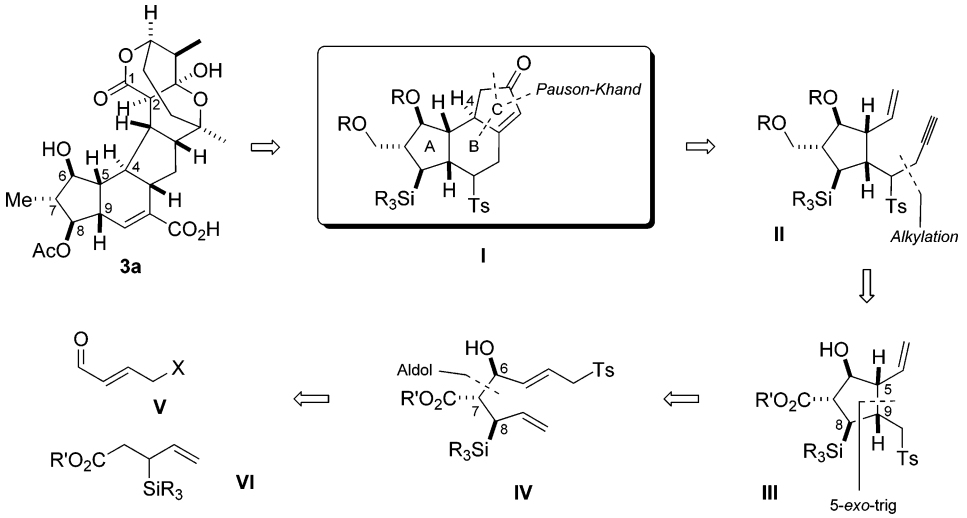
(27) (a) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552−4553. (b) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393−5407. (c) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 10, 1787−1790.

(28) (a) Stellfeld, T.; Bhatt, U.; Kalesse, M. *Org. Lett.* **2004**, *6*, 3889−3892. (b) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560−1561. (c) Clarke, P. A.; Grist, M.; Ebden, M. *Tetrahedron* Lett. **2004**, *45*, 927−929. (d) Clarke, P. A.; Cridland, A. P. *Org. Lett.* **2005**, *7*, 4221−4224.

(29) (a) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1037−1064. (b) Breczinski, P. M.; Stumpf, A.; Hope, H.; Krafft, M. E.; Casalnuovo, J. A.; Schore, N. E. *Tetrahedron* **1999**, *55*, 6797−6812. (c) Jeong, N.; Chung, Y. K.; Lee, S. H.; Yoo, S. E. *Synlett* **1991**, 204−206. (d) Hoye, T. R.; Suriano, J. A. *J. Org. Chem.* **1993**, *58*, 1659−1660. (e) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Huddecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220−223. (f) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801−2804. (g) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nisshizawa, M. *Synlett* **1999**, 771−773.

(30) Simpkins, N. S. *Sulfones in Organic Synthesis*; Tetrahedron Organic Chemistry Series; Pergamon Press: New York, 1993; Vol. 10.

SCHEME 6. Retrosynthetic Analysis of Hexacyclinic Acid A–B–C Tricyclic Skeleton

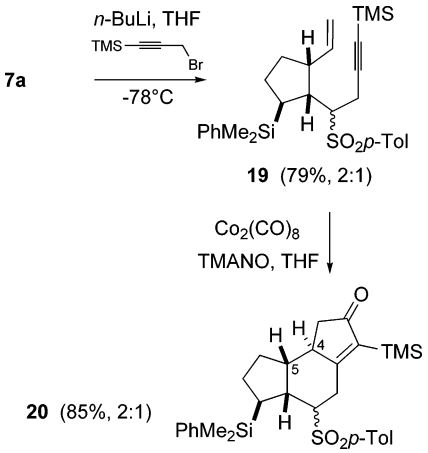


tion between C6, C7, and C8 stereogenic centers should be controlled efficiently.[31] The anti stereochemistry between C7 and C8 should thus be secured through a face-selective approach of the aldehyde on the β-silyl ester enolate, anti relative to the silicon group,[9a,d] through a transition-state model governed by $A_{1,3}$ strain.[32,33] In the meantime, the relative configuration between C6 and C7 would depend on the enolate geometry, with the (*E*)- and (Z)-enolates reported to produce predominantly the anti and syn isomers, respectively.

Following these considerations we started the synthesis of **I** by first investigating the intramolecular Pauson–Khand reaction on a model compound. Cyclopentane **7a**, described above, was thus alkylated using a TMS-protected propargyl bromide[34] to produce **19** in good yield as a 2:1 mixture (Scheme 7). This was then treated with $Co_2(CO)_8$ to form the alkyne–cobalt complex, which after removal of the solvents was treated with trimethylamine-*N*-oxide (TMANO·$2H_2O$) in THF to afford the desired tricyclic structure **20** as a 2:1 mixture of stereoisomers, possessing the requisite C4–C5-trans configuration. NOESY experiments on the major isomer of **20** showed unambiguously that the stereochemistry at C4 had been totally controlled during the enyne cyclization process,[29b] thus demonstrating that this methodology was suitable for elaboration and control of the stereochemistry of the contiguous C4, C5, C8, and C9 stereocenters of the A–B–C ring core of **3a**.

These encouraging results then prompted us to extend the strategy to the genuine system. We thus focused our attention on the synthesis of ester **IV** (Scheme 6) and control of the stereochemistry of the C6, C7, and C8 stereocenters through an aldol reaction between aldehyde **22** and ester **21**. Aldehyde **22** was easily prepared

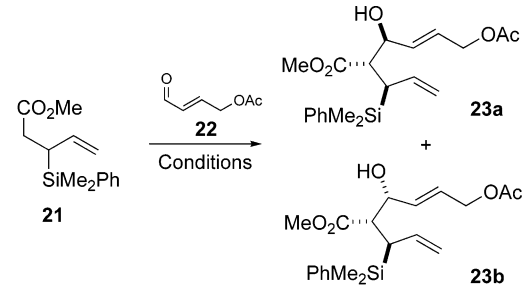
SCHEME 7. Pauson–Khand Cyclization of Enyne 19



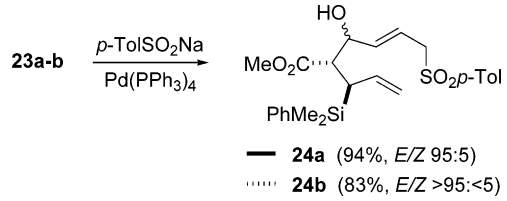
through a three-step procedure, including a reduction of the triple bond of commercial butyn-1,4-diol using $LiAlH_4$ (70% yield) followed by acetylation (80%) and oxidation of the remaining alcohol function using Dess–Martin periodinane.[35] The aldol reaction between **22** and the enolate of **21**, generated using LDA in THF, led to the aldol product as a 93:7 mixture of anti-syn **23b** and the desired anti-anti **23a** stereoisomers, respectively, in good yield (Scheme 8). The stereoselectivity observed in our case was in good agreement with previous reports from the literature,[32a] and although both stereoisomers could be isolated pure by chromatography, the amount of aldol **23a** formed under these conditions was clearly not suitable for our purpose. It was thus envisioned to reverse the ratio of stereoisomers by generating the (*Z*)- instead of (*E*)-enolate, known to produce predominantly the anti-syn isomer. This problem could be solved by generating the stereochemically defined enolate using LDA in a mixture of THF and HMPA.[36] When the reaction was carried out using LDA and 23% of HMPA in THF, a partial reversal of stereocontrol was observed with **23a** now formed predominantly in an unoptimized 40% yield.

(31) Fleming, I.; Kilburn, J. D. *J. Chem. Soc., Chem. Commun.* **1986**, 1198–1201.
(32) (a) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, *6*, 318–320. (b) Panek, J. S.; Beresis, R.; Xu F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341–7344. (c) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78–82. (d) Ward, R. A.; Procter G. *Tetrahedron* **1995**, *51*, 12821–12836.
(33) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
(34) Wu, R.; Schumm, J. S.; Pearson, D. L.; Tour, J. M. *J. Org. Chem.* **1996**, *16*, 6906–6921.
(35) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

SCHEME 8. Aldol Reaction between Ester 21 and Aldehyde 22



SCHEME 9. Preparation of Allyl Sulfone 24a,b



Anti-anti acetate **23a** was then converted into the corresponding sulfone **24a** using a palladium-catalyzed sulfonylation.[37] Similarly, anti-syn **23b** gave sulfone **24b** (Scheme 9). Both sulfones were then submitted to the above radical sulfonyl-mediated cascade to afford the corresponding cyclopentanes **25** and **26a,b** in excellent yield (Scheme 10). Interestingly, **24a** led to **25**[38] with complete stereocontrol, while its isomer **24b** gave an 82:18 mixture of two diastereomers **26a,b** which could not be separated through chromatography. The structure of stereoisomers **26a,b** was however assumed by analogy with the stereochemistry observed for the related substrates **7a**−**c** described in the preliminary studies (Table 1).

This difference of selectivity may be explained considering that with stereoisomer **24a** the 5-*exo*-trig cyclization likely proceeds through a chairlike transition state such as **A′** (Figure 3) similar to **TS-A** (Figure 1) in which all substituents are in a pseudoequatorial arrangement.[20,23] Such is not the case with stereoisomer **24b,** where the OH at C6 would be pseudoaxial in a similar chair conformation. It must be added that, as pointed out earlier by RajanBabu,[23] addition of alkyl radical onto olefins is

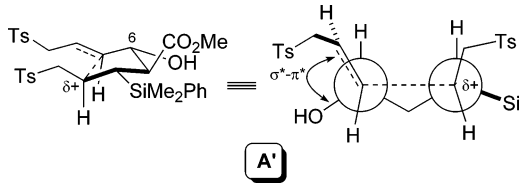
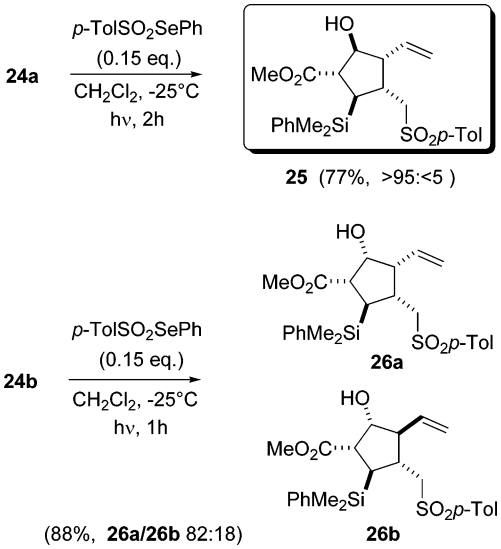


FIGURE 3. Transition-state model for the 5-*exo*-trig cyclization of precursor **24a**.

SCHEME 10. Sulfonyl Radical-Mediated 5-*exo*-Trig Cyclization of Dienes 24a,b



a nucleophilic process. Therefore, one may expect activation of the olefin π^* bond by the C6 allylic σ^*_{C-O} bond when it is properly aligned, as is the case with isomer **24a** in **TS-A′**.

Vinylcyclopentane **25**, having the correct relative configuration, was then converted in two steps into the MOM-protected diol **27** before being alkylated with the required propargylic bromide (Scheme 11). The conditions described above for the alkylation of model compound **7a** unfortunately led to no reaction. The same conditions applied to the less sterically congested TBDMS-protected alcohol **7c** also led to complete recovery of the starting material. After extensive experiments we finally found that using Schlosser's superbase,[39] deprotonation occurred to provide the sulfonyl carbanion which was alkylated to provide enyne **28** as a 4:1 ratio of two separable epimers at C10, albeit with modest conversion (35% with a 65% corrected yield). Enyne **28** was then treated under Pauson−Khand conditions as described above, providing the desired tricyclic compound **29** in 74% yield after filtration through a short pad of alumina. Extensive NOESY experiments on the major isomer of **29** (with stereochemistry as shown) established the trans relative configuration between C4 and C5, demonstrating that as before for **20** complete stereocontrol was observed during enyne cyclization. To conclude, using a straightforward approach relying on a radical 5-*exo*-trig cyclization/alkylation/intramolecular Pauson−Khand reaction

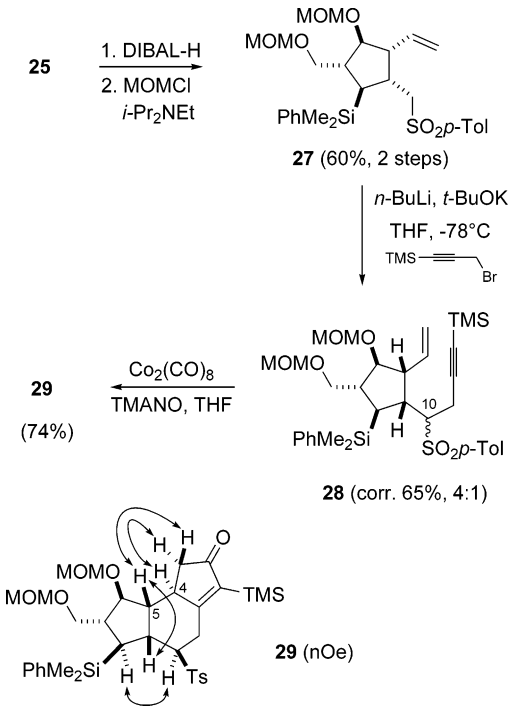
(36) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877.

(37) (a) Inomata, K.; Yamamoto, T.; Kotake, H. *Chem. Lett.* **1981**, 1357−1360. (b) Felpin, F.-X.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 6441−6446.

(38) It is also noteworthy that a low yield (26%) of **25** was first obtained upon chromatography over silica gel, demonstrating its sensitivity toward acid. This problem was finally overcome by adding 5% Et_3N to the eluent, leading after chromatography to pure **25** (77% yield). The acid sensitivity of **25** was attributed to the presence of the γ-silylcarbinol moiety, which is susceptible to react under these conditions. Examination of molecular models reveals that in **25** the Si−C8−C7−C6−O moiety adopts an ideal W conformation in which an interaction between the σ_{C8-Si} and a developing vacant p orbital at C6 (percaudal interaction) may be favored. Such an interaction (γ-silicon effect) was first proposed by Shiner et al. to rationalize the reaction rate acceleration observed during solvolysis of 1,3-*cis*- as compared to 1,3-*trans*-silylcylohexyl brosylates in CF_3CH_2OH, see. Shiner, V. J., Jr.; Ensinger, M. W.; Rutowske, R. D. *J. Am. Chem. Soc.* **1987**, *109*, 804−809.

(39) Schlosser, M. Superbases as Powerful Tools in Organic Syntheses. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: Weinheim, 1992; pp 227−271.

SCHEME 11. Preparation of the A−B−C Ring Core of Hexacyclinic Acid



we have been able to build up and control the relative configuration of the six stereogenic centers of the A−B−C ring core of hexacyclinic acid **3a** in only seven steps starting from the readily available β-silylester **21**.[32b−d]

Conclusion

In summary, we reported here on the remarkable effect of a silicon group on the 1,2- and 1,5-stereocontrol of radical 5-*exo*-trig cyclizations of hepta-1,6-dienes incorporating an allylsilane moiety. Such cyclizations at low temperature produced trisubstituted cyclopentanes having trans-cis stereochemistry as single diastereomers in excellent yield. This appeared to be specific to heptadienyl systems possessing a large group in the allylic position (i.e., a R_3Si or *t*-Bu group) since the same process carried out on a related precursor having a methyl group led to a very low level of stereocontrol and a mixture of the four possible stereoisomers. In contrast, the reaction performed on precursors having an alkoxy group in the allylic position gave complementary selectivity with the cis-cis isomer formed predominantly. Introduction of a strongly electron-withdrawing trifluoroacetate group led to complete stereocontrol under these conditions. Beckwith−Houk-type models were found to be appropriate to rationalize the stereochemistry observed. The stereoselectivity is assumed to be essentially steric in origin, as indicated by the complete stereocontrol observed during cyclization at 80 °C of precursor **9b**, having a large allylic *t*-Bu group. The value of this methodology was finally illustrated with a concise approach to the densely functionalized A−B−C ring core of hexacyclinic acid.

Experimental Section

General Procedure for 5-*exo*-Trig Cyclization of Dienes under Thermal Conditions. A mixture containing the diene (1 mmol), *p*-$TolSO_2SePh$ (0.15 mmol), and AIBN (0.10 mmol, added by portions every 1.5 h) in degassed benzene (0.013 M) was refluxed under a nitrogen atmosphere until TLC revealed completion of the reaction (more AIBN was added if necessary). The solvent was then evaporated, and the residue was purified by chromatography on silica gel.

General Procedure for 5-*exo*-Trig Cyclization of Dienes through Irradiation. A mixture containing the diene (1 mmol) and *p*-$TolSO_2SePh$ (0.15−0.50 mmol) in degassed solvent (0.013 M) under a nitrogen atmosphere was irradiated with a sun lamp (300 W) placed 10−15 cm from the flask until TLC revealed completion of the reaction. The solvent was then evaporated, and the residue was purified by chromatography on silica gel.

Dimethylphenyl-[2-(toluene-4-sulfonylmethyl)-3-vinylcyclopentyl]silane (7a). Following the general procedure described above (irradiation), diene **6a** (43 mg, 0.11 mmol) and *p*-$TolSO_2SePh$ (8.4 mg, 0.03 mmol) in degassed $CHCl_3$ (8.5 mL) were irradiated for 30 min at − 50 °C. Purification by chromatography (petroleum ether/EtOAc 9/1) afforded **7a** as a pale yellow oil (34 mg, 84%). IR (neat) ν = 3068, 2951, 2864, 1597, 1426, 1315, 1301, 1249, 1149, 1113, 812, 772, 735, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.61 (d, J = 8.3 Hz, 2 H), 7.44 (m, 2 H), 7.35 (m, 3 H), 7.31 (d, J = 8.3 Hz, 2 H), 5.61 (ddd, J = 17.1, 10.4, 8.9 Hz, 1 H), 5.07 (dd, J = 10.4, 2.1 Hz, 1 H), 5.01 (ddd, J = 17.1, 2.1, 0.8 Hz, 1 H), 3.00 (dd, ABX, J_{AB} = 14.2 Hz, J_{AX} = 9.7 Hz, $\Delta\nu/J$ = 9, 1 H), 2.82 (m, 1 H), 2.79 (dd, ABX, J_{AX} = 9.7 Hz, J_{BX} = 2.7 Hz, $\Delta\nu/J$ = 9, 1 H), 2.44 (s, 3 H), 2.38 (m, 1 H), 1.89 (m, 1 H), 1.64−1.53 (m, 3 H), 1.15 (m, 1 H), 0.26 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 144.7, 138.3, 137.9, 137.6, 134.3, 129.5, 128.6, 128.4, 128.3, 128.2, 117.5, 57.3, 47.3, 39.9, 31.9, 28.2, 25.3, 22.0, −3.4, −4.9. MS (FAB^+) m/z = 421 (M + Na^+, 20), 399 (M + H^+, 4), 398 (M, 2), 383 (17), 321 (100). HRMS (FAB^+) calcd for $C_{23}H_{30}O_2SSi$ + Na^+: 421.1633. Found: 421.1644. Anal. Calcd for $C_{23}H_{30}O_2Ssi$: C, 69.30; H, 7.59. Found: C, 69.16; H, 7.62.

Dimethylphenyl-[2-(toluene-4-sulfonylmethyl)-3-vinylcyclopentyl]silane (8a). Following the general procedure (thermal conditions), diene **6a** (400 mg, 1.00 mmol), *p*-$TolSO_2SePh$ (46.7 mg, 0.15 mmol), and AIBN (14.2 mg, 0.10 mmol) in degassed benzene (75 mL) were refluxed for 10 h. The solvent was then evaporated, and the residue (86:14 mixture of the two diastereoisomers **7a/8a**) was purified by chromatography (petroleum ether/EtOAc 9/1) to afford a pale yellow oil (35 mg, 9% for pure **8a**; **7a** and **8a** were isolated in 69% overall yield). **8a**: IR (neat) ν = 3068, 2951, 1637, 1597, 1427, 1316, 1301, 1250, 1147, 1112, 1087, 1018, 997, 734, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.60 (d, J = 7.9 Hz, 2 H), 7.40−7.27 (m, 7 H), 5.54 (ddd, J = 17.3, 10.2, 7.9 Hz, 1 H), 4.96 (br d, J = 16.9 Hz, 1 H), 4.86 (br d, J = 10.2 Hz, 1 H), 2.92 (dd, J = 14.1, 8.8 Hz, 1 H), 2.83 (dd, J = 14.1, 3.2 Hz, 1 H), 2.77 (m, 1 H), 2.45 (s, 3 H), 2.05 (m, 1 H), 1.80−1.60 (m, 2 H), 1.57−1.37 (m, 2 H), 1.08 (m, 1 H), 0.23 (s, 6 H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ = 144.2, 141.4, 137.7, 137.1, 133.9, 129.6, 129.0, 128.2, 128.0, 127.8, 113.6, 61.3, 49.1, 41.1, 33.3, 32.6, 27.2, 21.6, −4.1, −5.1. MS (FAB^+) m/z = 421 (M + Na^+, 22), 383 (19), 321 (100), 211 (38). HRMS (FAB^+) calcd for $C_{23}H_{30}O_2SSi$ + Na^+: 421.1633. Found: 421.1630.

Methyl 6-Acetoxy-3-hydroxy-2-(1-(dimethyl(phenyl)-silyl)allyl)hex-4-enoate (23a). A solution of LDA (8.32 mmol) in dry THF (22.7 mL) under a nitrogen atmosphere was cooled at −78 °C, and HMPA (6.8 mL) was added. To this vigorously stirred solution was added dropwise ester **21** (2.07 g, 8.32 mmol) in THF (1 mL). After 30 min at −78 °C, aldehyde **22** (1.12 g, 8.74 mmol) in THF (1 mL) was added dropwise to the deep orange solution. The mixture was stirred 1 h at this temperature and then quenched with glacial acetic acid (1 mL). The mixture was then allowed to warm to room temperature, and an aqueous solution of NH_4Cl was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were then washed with aqueous $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and filtered, and the solvents were concentrated under vacuum. Purification of the crude material (**23a/23b** 65:35) by chroma-

tography gave a pale yellow oil [**23a** (661 mg, 21%), **23b** (602 mg, 19%), 40% overall yield]. **23a**: IR (neat) ν = 3507, 3070, 2952, 2902, 1739, 1712, 1626, 1428, 1380, 1361, 1247 1113, 1027, 969, 702, 656 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.47 (m, 2 H), 7.33 (m, 3 H), 5.80−5.60 (m, 2 H), 5.57 (dt, J = 16.8, 10.1 Hz, 1 H), 5.07 (br dd, J = 7.3 Hz, 1 H), 5.01 (br dd, J = 13.4 Hz, 1 H), 4.49 (d, J = 5.5 Hz, 2 H), 4.32 (m, 1 H), 3.25 (s, 3 H), 3.05 (d, J = 9.5 Hz, 1 H), 2.57 (m, 1 H), 2.53 (m, 1 H), 2.02 (s, 3 H), 0.32 (s, 3 H), 0.23 (s, 3 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ = 173.9, 170.4, 136.3, 135.6, 134.9, 134.1, 129.0, 127.4, 124.5, 116.1, 69.7, 63.9, 51.0, 49.5, 33.2, 20.7, −3.4, −5.2. MS (FAB$^+$) m/z = 399 (M + Na$^+$, 100), 247 (12). HRMS (FAB$^+$) calcd for $C_{20}H_{28}O_5Si$ + Na$^+$: 399.1603. Found: 399.1605.

Methyl 6-Acetoxy-3-hydroxy-2-(1-(dimethyl(phenyl)-silyl)allyl)hex-4-enoate (23b). A solution of LDA (8.6 mmol) in dry THF (10 mL) under a nitrogen atmosphere was cooled at −78 °C, and ester **21** (1.94 g, 7.8 mmol) in THF (4 mL) was added dropwise. After 45 min at −78 °C, aldehyde **22** (1.0 g, 7.8 mmol) in THF (2 mL) was added dropwise, and the mixture was stirred 30 min at this temperature and then quenched with glacial acetic acid (1 mL). The mixture was then allowed to warm to room temperature, and an aqueous solution of NH_4-Cl was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were then washed with aqueous $NaHCO_3$, saturated NaCl, dried over $MgSO_4$, and filtered, and the solvents were concentrated under vacuum. Purification of the crude material (**23b/23a** 93:7) by chromatography (petroleum ether/ethyl acetate 8/2 then 7/3) gave **23b** a pale yellow oil (2.02 g, 69% yield). IR (neat) ν = 3496, 3070, 1736, 1624, 1248, 1196, 1145, 1113, 1084, 1026, 971, 903, 837, 817, 702, 657 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.46 (m, 2 H), 7.33 (m, 3H), 5.81 (dd, J = 15.5, 6.4 Hz, 1 H), 5.71 (dt, J = 15.5, 5.7 Hz, 1 H), 5.55 (dt, J = 17.0, 10.6 Hz, 1 H), 4.99 (dd, J = 10.2, 1.9 Hz, 1 H), 4.86 (dd, J = 17.3, 1.5 Hz, 1 H), 4.52 (d, J = 5.7 Hz, 2 H), 4.30 (q, J = 5.7 Hz, 1 H), 3.36 (s, 3 H), 2.86 (dd, J = 11.3, 5.7 Hz, 1 H), 2.37 (br d, J = 4.5 Hz, 1 H), 2.23 (t, J = 10.9 Hz, 1 H), 2.03 (s, 3 H), 0.30 (s, 3 H), 0.26 (s, 3 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ = 172.8, 170.5, 136.6, 136.2, 134.2, 132.2, 129.0, 127.5, 126.5, 115.3, 72.4, 64.1, 51.2, 50.9, 34.2, 20.8, −3.7, −4.6. MS (FAB$^+$) m/z = 399 (M + Na$^+$, 100), 359 (6), 327 (7), 299 (11), 288 (16), 247 (33), 221 (17), 207 (22). Anal. Calcd for $C_{20}H_{28}O_5Si$: C, 63.80; H, 7.50. Found: C, 63.99; H, 7.75.

General Procedure for the Preparation of Allyl Sulfones. To a solution of sodium *p*-tolylsulfinate tetrahydrate (1.1 mmol) in methanol was successively added a solution of allyl acetate or allyl bromide (1 mmol) in THF and a solution of $Pd(PPh_3)_4$ (0.05 mmol) in THF at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature until disappearance of the starting material (TLC) and then treated with KCN (0.2 mmol), and the solvents were evaporated under vacuum. The residue was then purified by chromatography on silica gel.

Methyl 3-Hydroxy-2-(1-(dimethyl(phenyl)silyl)allyl)-6-tosylhex-4-enoate (24a). 24a was prepared according to the general procedure above. Usual workup and chromatography (petroleum ether/EtOAc 6/4) yielded **24a** (*E*/*Z*: 95:5) as a yellow viscous oil (785 mg, 94%). IR (neat) ν = 3500, 3071, 2926, 1732, 1625, 1596, 1317, 1302, 1248, 1138, 1113, 1086, 702, 667 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.69 (m, J = 8.3 Hz, 2 H), 7.47 (m, 2 H), 7.34 (m, 3 H), 7.28 (d, J = 7.9 Hz, 2 H), 5.58 (m, 3 H), 5.53 (m, 2 H), 4.27 (br d, J = 9.4 Hz, 1 H), 3.71 (d, J = 6.4 Hz, 2 H), 3.29 (s, 3 H), 3.24 (d, J = 9.8 Hz, 1 H), 2.53 (m, 2 H), 2.38 (s, 3 H), 0.34 (s, 3 H), 0.24 (s, 3 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ = 173.7, 144.2, 140.9, 136.1, 135.5, 135.4, 133.8, 129.4, 129.4, 128.9, 128.0, 127.9, 127.3, 116.7, 115.9, 69.8, 59.0, 51.1, 49.1, 33.2, 21.2, −3.5, −5.3. MS (FAB$^+$) m/z = 495 (M + Na$^+$, 100), 455 (5), 395 (3), 247 (6), 213 (14). HRMS (FAB$^+$) calcd for $C_{25}H_{32}O_5SSi$ + Na$^+$: 495.1637. Found: 495.1631.

(3-(Methoxymethoxy)-2-((methoxymethoxy)methyl)-5-(tosylmethyl)-4-vinylcyclopentyl)dimethyl(phenyl)-silane (27). Cyclopentane **25** (0.91 g, 1.93 mmol) was dissolved in dry CH_2Cl_2 (25 mL) under a nitrogen atmosphere, and the solution was cooled to −78 °C. A 1 M solution of DIBAL-H in CH_2Cl_2 (12.5 mL, 12.5 mmol) was then added dropwise, and the mixture was stirred for 3 h at this temperature and then quenched with MeOH. The reaction mixture was then allowed to warm to room temperature, and an aqueous solution of $NaHCO_3$ was added. The mixture was filtered through Celite, and the gelatinous precipitate was washed extensively with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was finally dissolved in dry CH_2Cl_2 (75 mL) under a nitrogen atmosphere, and diisopropylethylamine (4.4 mL, 25 mmol) was added. The flask was cooled to 0 °C, and MOMCl (1.4 mL, 15 mmol) was added dropwise. The solution was stirred at room temperature overnight and then poured into a $NaHCO_3$ solution. The layers were separated, and the aqueous solution was extracted with dichloromethane. The combined organic layers were washed with NH_4Cl and brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. Purification by chromatography (petroleum ether/EtOAc/NEt_3 85/10/5) afforded **27** as a pale yellow oil (615 mg, 60%, 2 steps). IR (neat) ν = 2924, 1314, 1300, 125, 1148, 1110, 1088, 814, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.65 (d, J = 8.3 Hz, 2 H), 7.50 (m, 2 H), 7.38 (m, 3 H), 7.31 (d, J = 8.3 Hz, 2 H), 5.58 (dt, J = 16.9, 9.4 Hz, 1 H), 5.12 (m, 2 H), 4.61 (d, J = 3.0 Hz, 2 H), 4.54 (s, 2 H), 3.93 (br t, J = 3.8 Hz, 1 H), 3.38 (m, 1 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 3.15 (dd, J = 9.4, 7.2 Hz, 1 H), 3.08 (dd, J = 13.9, 7.5 Hz, 1 H), 2.93 (dd, J = 14.3, 4.9 Hz, 1 H), 2.80 (m, 2 H), 2.72 (m, 1 H), 2.45 (s, 3 H), 2.14 (m, 1 H), 1.22 (t, J = 8.3 Hz, 1 H), 0.38 (s, 6 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ = 144.2, 137.4, 137.1, 134.7, 133.8, 129.5, 129.1, 127.8, 127.8, 119.1, 96.2, 95.0, 83.8, 68.9, 56.3, 55.1, 55.0, 53.4, 48.0, 37.4, 30.1, 21.4, −4.2, −5.1. MS (FAB$^+$) m/z = 555 (M + Na$^+$, 52), 501 (9), 471 (9), 439 (3), 425 (6), 379 (3), 305 (7), 275 (5), 213 (33), 179 (5), 149 (54), 135 (100). HRMS (ES$^+$) calcd for $C_{28}H_{40}O_6SSi$ + Na$^+$: 555.2213. Found: 555.2213.

Enyne (28). To a stirred solution of silylcyclopentane **27** (420 mg, 0.81 mmol) in dry THF (3 mL) under an argon atmosphere was added dropwise a solution of sublimed *t*-BuOK (112 mg, 1.00 mmol) in THF (9 mL) at −78 °C. A 2.5 M solution of *n*-BuLi in hexanes was then added dropwise at this temperature, and the red-brown solution was stirred for 1 h at −78 °C. 3-Bromo-1-trimethylsilylpropyne[34] was added dropwise below −78 °C, the solution was stirred for 1 h before being quenched with MeOH (1 mL), and the mixture was allowed to warm to 0 °C. An aqueous solution of NH_4Cl was added, and the layers were separated. The aqueous layer was extracted with ether; the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered, and the solvents were removed under vacuum. Purification by chromatography (petroleum ether/EtOAc/NEt_3 85/10/5) afforded a pale yellow oil (104 mg of the major diastereomer was isolated; 180 mg (35%) of a combined fraction of both diastereomers, and 131 mg of starting **27** was recovered, 65% corrected yield). **28**: IR (neat) ν = 2954, 2177, 1596, 1427, 1312, 1250, 1146, 1109, 1086, 761, 702, 662 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) *Major* δ = 7.69 (d, J = 8.3 Hz, 2 H), 7.61 (m, 2 H), 7.38 (m, 3 H), 7.33 (d, J = 8.3 Hz, 2 H), 5.93 (dt, J = 17.0, 10.1 Hz, 1 H), 5.12 (dd, J = 10.2, 2.0 Hz, 1 H), 5.05 (dd, J = 17.1, 1.2 Hz, 1 H), 4.56 (s, 2 H), 4.45 (s, 2 H), 4.09 (dd, J = 8.9, 7.0 Hz, 1 H), 3.37 (dd, J = 10.0, 3.5 Hz, 1 H), 3.33−3.20 (m, 2 H), 3.26 (s, 6 H), 3.04 (br dd, 1 H), 2.99 (m, 1 H), 2.63 (dd, J = 18.8, 4.5 Hz, 1 H), 2.46 (m, 1 H), 2.44 (s, 3 H), 2.04 (m, 1 H), 1.67 (dd, J = 8.3, 4.5 Hz, 1 H), 0.50 (s, 3 H), 0.48 (s, 3 H), 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) *Major* δ = 144.4, 137.6, 136.6, 136.0, 134.2, 129.8, 129.1, 128.6, 127.7, 119.0, 103.0, 96.3, 95.8, 87.2, 82.9, 68.0, 64.0, 55.3, 55.2, 55.1, 48.3, 39.8, 24.1, 21.6, 17.0, −0.3, −3.1, −4.9. *Minor* δ = 144.4, 137.5, 136.6, 136.1, 134.1, 129.6, 129.3, 128.7, 128.0, 117.5, 103.3, 96.2, 95.1, 87.2, 86.1, 69.7, 64.0, 55.3, 55.2, 55.1, 48.4, 40.7, 27.4, 21.6, 18.0, −0.2, −4.8, −4.9. MS (FAB$^+$) m/z = 665 (M + Na$^+$, 7), 425 (6), 363 (4), 305 (5), 259

(4), 213 (23), 165 (13), 151 (17), 139 (27), 137 (15), 135 (100), 133 (49). HRMS (ES^+) calcd for $C_{34}H_{50}O_6SSi_2 + Na^+$: 665.2750. Found: 665.2764.

Tricyclic Ketone (29). $Co_2(CO)_8$ (41.5 mg, 0.121 mmol) was added to enyne **28** (65 mg, 0.101 mmol) in dry ether (3 mL) at room temperature. The reaction mixture was stirred for 1 h and then concentrated under vacuum. The crude mixture was then dissolved in THF (3 mL), and $TMANO{\cdot}2H_2O$ (73.8 mg, 0.666 mmol) was added by portions. The reaction mixture was stirred for 3 h at room temperature, filtered, and concentrated under vacuum. Purification through a short pad of neutral alumina (CH_2Cl_2) yielded **29** as a yellow oil (50 mg, 74%). IR (neat) ν = 2950, 1687, 1549, 1302, 1280, 1248, 1146, 1110, 840, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.70 (d, J = 7.9 Hz, 2 H), 7.42−7.26 (m, 7 H), 4.67 (s, 2 H,), 4.43 (q, J = 6.4 Hz, 2 H), 4.11 (m, 1 H), 3.40−3.27 (m, 3 H), 3.38 (s, 3 H), 3.30 (s, 3 H), 3.07−2.95 (m, 2 H), 2.75−2.42 (m, 3 H), 2.50 (s, 3 H), 2.13 (m, 1 H), 2.05 (m, 1 H), 1.96 (m, 1 H), 1.79 (m, 1 H), 0.37 (s, 3 H), 0.35 (s, 3 H), 0.03 (s, 9 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ = 212.1, 184.5, 144.8, 139.1, 138.5, 137.7, 134.0, 129.9, 129.1, 128.4, 127.7, 96.9, 96.6, 85.9, 67.8, 63.8, 55.9, 55.3, 52.9, 49.4, 42.8, 42.7, 39.6, 29.9, 24.6, 21.6, −0.9, −3.2, −4.6. HRMS (ES^+) calcd for $C_{35}H_{50}O_7SSi_2 + Na^+$: 693.2718. Found: 693.2714.

Acknowledgment. This work was supported by the Ministère de la Recherche et de la Technologie through a Ph.D. grant to P.J. Y.L. gratefully acknowledges the Institut Universitaire de France and the CNRS for financial support. Finally, we thank Prof. M.-P. Bertrand (University of Marseille) and Prof. M. Malacria (University Paris-VI) for stimulating discussions.

Supporting Information Available: Experimental procedures and structural data for new compounds; X-ray crystallographic data for compounds **7b**, **11**, and **18** (cif files). This material is available free of charge via the Internet at http://pubs.acs.org.

JO051062G