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Transannular Radical Cascade as an Approach to the Diastereoselective Synthesis of Linear Triquinane**

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Diastereoselective constructions of polycyclic structures such as triquinanes by 5-*exo*-radical-cyclization cascade reactions that start from a templating ring are well-known;[1] from acyclic systems only a few such reactions involve diastereoselective processes.[2] However, transannular cyclizations, which are nowadays frequently used as a key step in the synthesis of polycyclic frameworks,[3] have been poorly described as an efficient means of reaching linear triquinane systems diastereoselectively. There is only one specific example reported by Winkler in which linear triquinanes were obtained as a mixture of diastereomers, from suitably substituted cycloocta-1,5-dienes, by a unique transannular process.[4]

During the last decade, we have been interested in the development of highly chemo-, regio-, and stereoselective cascade processes which rely on radical transannular reactions.[5] The diastereoselective total synthesis of the protoilludane *epi*-illudol, which has an angularly fused 4,6,5-tricyclic framework, was achieved by a cascade of radical transannular cyclizations from a (bromomethyl)dimethylsilyl (BMDMS) ether of a cycloundeca-4,8-dien-1-yne (Scheme 1).[5b] By following the same type of cascade, we believed that switching the BMDMS-ether tether from the C-1 atom to the C-4 atom should now lead to a triquinane skeleton of type **1**. We anticipated that the disubstituted double-bond geometry would be crucial for the behavior of the transannular cascade. In fact, when the *Z*,*E* precursor **2** was submitted to radical cyclization conditions, the generated vinyl radical cyclized regioselectively in a 6-*endo* mode, leading to the 6,7-bicyclic compound **4**(Scheme 1).[5c] In contrast, we report herein the stereoselective construction of a linear triquinane through an unprecedented cascade of diastereoselective transannular cyclizations from an *E*,*E* precursor.

Access to precursor **3** was envisaged by following a similar strategy to that developed for the eleven-membered ring **2**, by using Nozaki-Hiyama-Kishi-Takai (NHKT) macrocyclization as the key step. Thus, *E*-heptenal **6** (as a common precursor),[6] was subjected to the mild Horner-Wadsworth-Emmons olefination conditions described by Masamune and Roush[7] to furnish, after tetrabutylammonium fluoride (TBAF) mediated cleavage of the resulting silylated ether, the *E*-α,β-unsaturated ester **7**. Dess-Martin oxidation[8] of the homoal-

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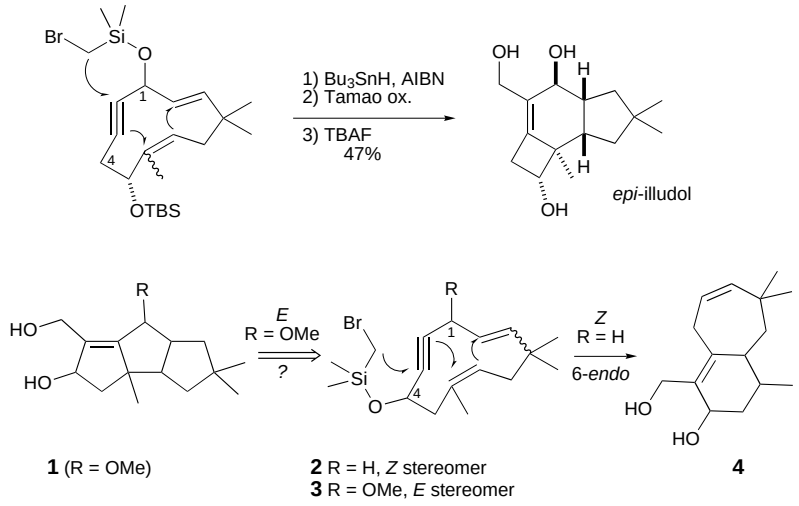


Scheme 1. Transannular radical cyclizations cascade reactions. TBS = *tert*-butyldimethylsilyl.

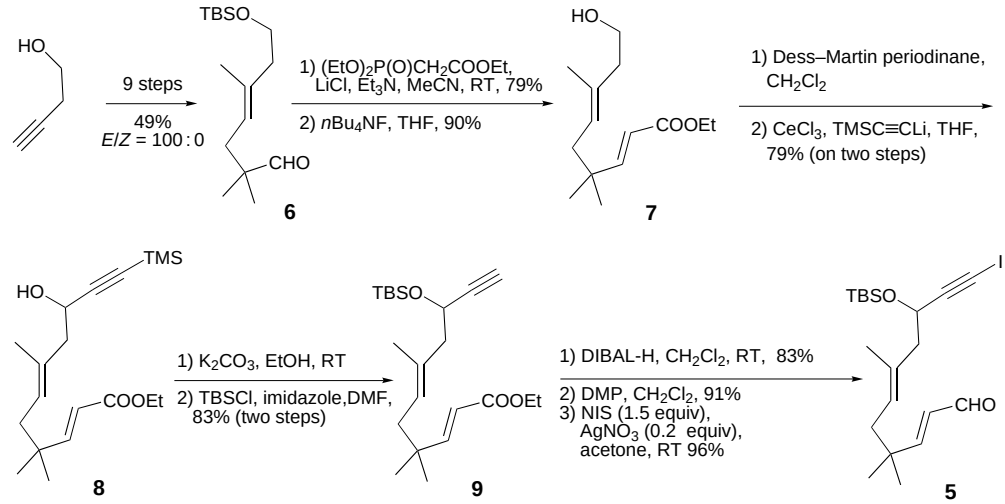
lylic alcohol moiety, followed by condensation of the in situ generated organocerium derivative of trimethylsilylacetylene,[9] with the crude β,γ-unsaturated aldehyde thus provided ynol **8**. A sequential deprotection of the alkyne/O-silylation led to the propargylic silyl ether **9**. Reduction of **9** and subsequent oxidation of the resulting allylic alcohol gave the expected undecadienynal, which was submitted to mild iodination conditions[10] to give the iodoalkyne **5** (Scheme 2).

Carefully controlled slow addition of iodoalkyne **5** in THF to a suspension of chromium chloride (7 equiv) in THF produced the desired macrocyclic propargylic alcohol **10** as a 2:1 mixture of diastereomers in 88% yield (Scheme 3). These diastereomers were particularly difficult to separate, however, we could enrich the mixture to a 3:1 ratio. Then, a methylation–desilylation sequence afforded the expected propargylic alcohol.

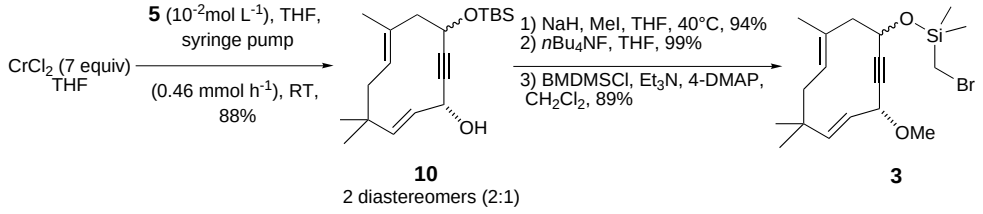
The BMDMS ether **3**, prepared under classical silylation conditions, was subjected to reaction with Ph_3SnH–AIBN (AIBN = azobisisobutyronitrile), followed by Tamao oxidation to lead to the 5,5,5-tricyclic triquinane framework **1** in 45% yield diastereoselectively (Scheme 4), along with a bicyclic diol **11** as a 2:1 mixture of diastereomers in 12% yield.

Full characterization by ^1H and ^{13}C NMR spectroscopy, COSY, NOE (Scheme 5), IR, MS, HRMS, and elemental analysis unambiguously supports the proposed structures for **1** and **11**.

The formation of triquinane **1** results from the now well-established 5-*exo-dig* process[5] from the initial α-silyl radical **A** to the vinyl radical **B**, which then undergoes the transannular tandem [5-(π-*endo*)-*exo-trig*/8-(π-*exo*)-*endo-trig*]/[5-*exo-trig*/5-*endo-trig*], allowing the consecutive formation of the tricyclic radical **C**; this finally cyclizes to form the expected tetracyclic radical **D**. The latter follows two competitive processes: a stannane reduction–Tamao oxidation sequence leading to **1** or, alternatively, a minor β-fragmentation process provides the stabilized α-methoxy and allylic radical **E**. This latter is reduced in an *endo* mode to give the



Scheme 2. Synthesis of precursor **5**. DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, NIS = *N*-iodosuccinimide



Scheme 3. NHKT macrocyclization of precursor **5** and functional modifications to precursor **3**.

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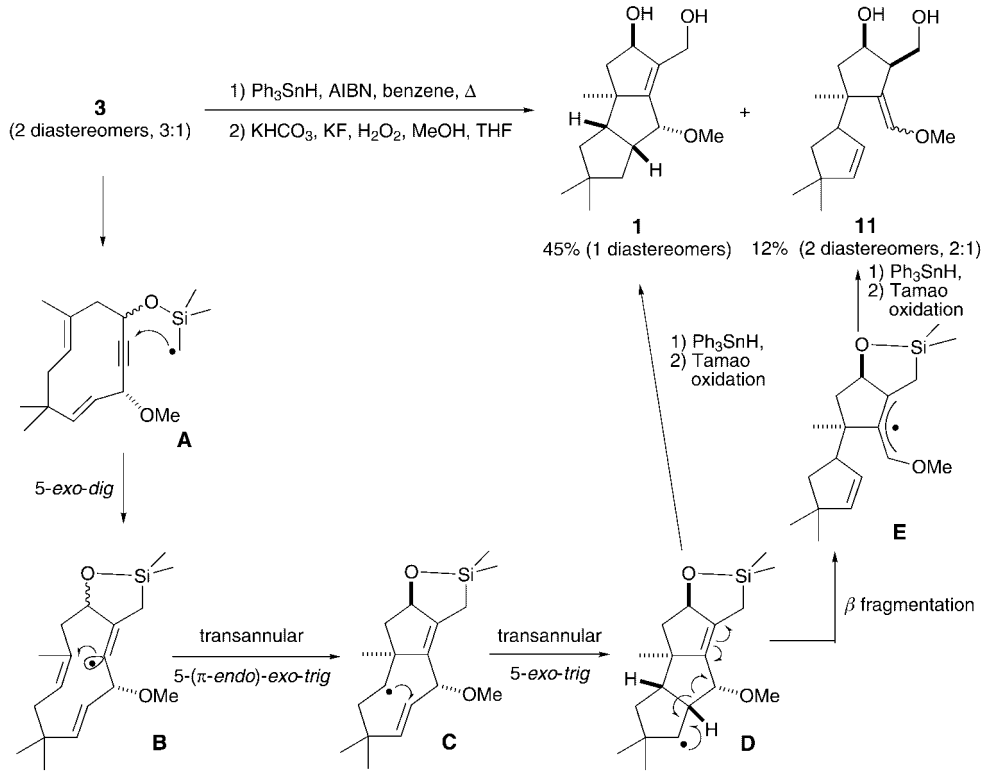
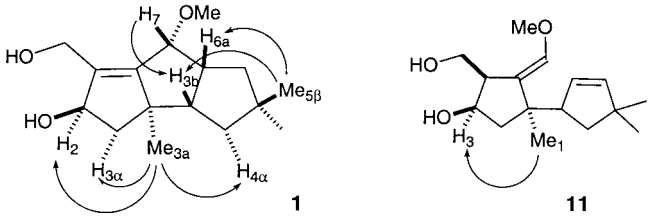


Scheme 4. Radical transannular cascade.



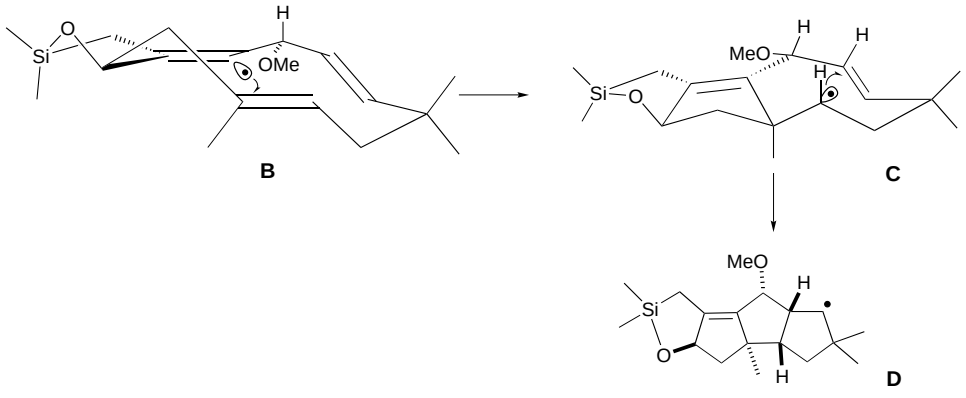
Scheme 5. NOE measurements for stereochemical assignments of **1** and **11.**

major diastereomer **11**, which possesses the less constrained *E* double bond (Scheme 4).

A model accounting for the stereoselectivity is proposed in Scheme 6. First, cyclization from the major diastereomer **3** leads to the formation of **B**, in which the heterosilane is *anti* to the methoxy moiety. When the vinylic methyl group is positioned on the β-face, inside the strained macrocycle, the steric hindrance created would lead to the predominance of the proposed conformation **B**, where the methyl group is outside. Thus, the *syn* relationship between methyl and methoxy groups could be rationalized. A final 5-*exo-trig* transannulation (shown on **C**), directed by thermodynamic requirements, led to the *cis-anti-cis* triquinane framework of **D**.

The difference of regioselectivity between the cyclizations of vinyl radicals created from precursor **2** and **3** undoubtedly results from the geometric strain generated by the stereochemistry of the double bond. The 6-*endo* transannular cyclization, which creates a seven-membered unsaturated ring, is allowed when this *endo*-double-bond stereochemistry is *Z*, as in dienyne **2**[5c] and instead, would become forbidden when an *E* double bond is included, as in triquinane precursor **3**. This geometric factor exhibits a tremendous influence on the transannular cascade behavior and becomes much more important than the position of the methyl group on the accepting double bond.

In summary, we have reported the first example of a triquinane generation by a diastereoselective series of transannular radical cyclizations. Our synthetic transannular strategy was so efficient that, by using the same cycloundecadienyne framework and just moving the radical trigger from one propargylic position to the other, we have a completely selective entry to either the protoilludane[4b] or the triquinane family.



Scheme 6. Model for stereoselectivity.

Experimental Section

1: To a degassed solution of the BMDMS ether **3** (154 mg, 0.4 mmol) as a 3:1 mixture of diastereomers in 14 mL of dry benzene heated under reflux, was added a solution of Ph_3SnH (182 mg, 0.52 mmol) and AIBN (20 mg, 0.12 mmol) in 4 mL of dry and degassed benzene by syringe pump (2.12 mL h^{-1}). At completion of the addition, and when all starting material was consumed, the benzene was removed under vacuum and the stannylated derivatives were precipitated by stirring in pentane at 0 °C. Filtration twice through celite furnished a residue, which was poured into a mixture of THF/MeOH (1:1, 6 mL) with of $KHCO_3$ (248 mg,

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2.48 mmol), KF (93 mg, 1.6 mmol), and a solution of H_2O_2 (35%, 4 mL). After heating for 1 h at 70°C, the reaction mixture was cooled to room temperature, filtered through Celite, and rinsed 3 times with ethyl acetate. The aqueous phase was extracted twice more with ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified on a silica-gel column, eluting with 3% MeOH in CH_2Cl_2 to afford 47 mg of **1** (45%) and 13 mg of cyclopentane **11** (12%).

1: Yield: 45%; ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): $\delta = 5.27$ (t, $J = 6.6$ Hz, 1H; H-2), 4.47 (d, $J = 12.6$ Hz, 1H; CH_2OH,), 4.32 (d, $J = 12.6$ Hz, 1H; CH_2OH), 4.03 (d, $J = 6.4$ Hz, 1H; H-7), 3.15 (s, 3H; OMe), 2.88 (m, 1H, H-6a), 2.38 (dd, $J = 11.3$ Hz, $J = 9.5$ Hz, 1H; H-3b), 2.36 (dd, $J = 12.1$ Hz, $J = 6.4$ Hz, 1H; H-3), 1.68 (dd, $J = 12.1$ Hz, $J = 10.7$ Hz, 1H; H-6), 1.53 (dd, $J = 11.9$ Hz, $J = 7.8$ Hz, 1H; H-3′), 1.32 (d, $J = 9.6$ Hz, 2H; H-4), 1.24 (dd, $J = 8.4$ Hz, $J = 3.5$ Hz, 1H; H-6), 1.07 (s, 3H; H-5α), 1.00 (s, 3H; H-3a), 0.92 ppm (s, 3H; H-5β); ^{13}C NMR ($CDCl_3$, 50 MHz, 25°C) $\delta = 154.8$ (C-7a), 135.4 (C-1), 81.3 (C-7), 75.6 (C-2), 58.3 (CH_2OH), 56.3 (CH_3O), 55.0 (C-3), 53.6 (C-3b), 50.8 (C-3a), 49.9 (C-6a), 43.2 (C-5), 41.2 (C-6), 38.2 (C-4), 29.2 (CH_3-5), 27.4 (CH_3-5), 23.4 ppm (CH_3-3a); IR (neat)$\tilde{\nu}$ 3450 (br), 2940, 2850, 1650 (br), 1455, 1360, 1090, 995, 760 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{26}O_3$ ($M = 266.381$ g mol^{-1}): C 72.14, H 9.83; found : C 72.11, H 9.80; MS (CI, CH_4): m/z (%) 266 (M^+, 4%), 265 (M^+-1, 7%), 249 (M^+-OH, base peak), 231 (47%), 217 (35%).

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