A New Cyclization Reactions Cascade:Ene Type, [2 + 2 + 2], [4 + 2]. Stereoselective Formation of Six Carbon–Carbon Bonds and Four Rings in a One-Pot Sequence

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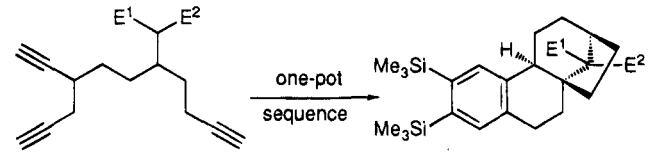
In recent years, transition metal-mediated cyclization of substrates containing two or more unsaturations have provided new catalytic strategies for the construction of complex polycyclic molecules.[1,2] Toward this aim, we have disclosed a stereoselective approach[3] to the basic framework of tetracyclic diterpenes of phyllocladane and kaurane families in a sequence involving three consecutive cycloaddition reactions: a Pd(0)-assisted [3 + 2] annulation reaction,[4] a [2 + 2 + 2] Co(I)-catalyzed cyclotrimerization,[5] and finally, an intramolecular [4 + 2] cyclization.

An ultimate goal of such an approach would be the discovery of a single transition metal mediating a one-pot sequence of cyclizations.[6] Our finding that Co(I) species catalyze the cycloisomerization of ϵ-acetylenic β'-alkyl β-keto esters with the diastereoselective generation of highly functionalized methylenecyclopentanes[7,8] suggested the feasibility of such a strategy: ene type reaction, [2 + 2 + 2], and [4 + 2] which would provide an unprecedented entry to substituted tetracyclic diterpenes.

Here, we report an entirely novel and rapid access to the basic skeleton of the phyllocladane family *via* a one-pot sequence catalyzed by (η^5-cyclopentadienyl)dicarbonylcobalt(I) [$CpCo(CO)_2$] creating six carbon–carbon bonds in a chemo-, regio-, and stereoselective manner (Scheme 1) from an acyclic polyunsaturated precursor owning three uncontrolled centers.

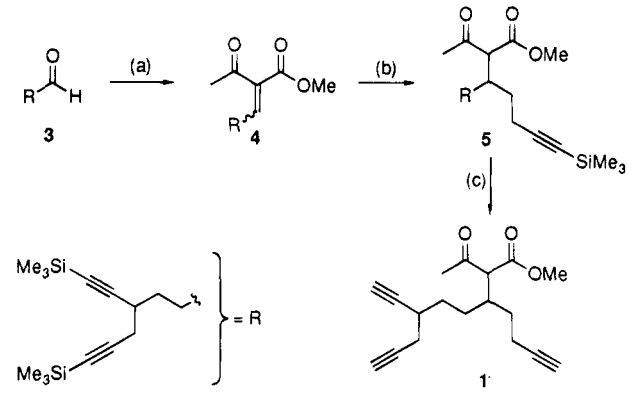
Scheme 1



1 2

$E^1 = CO_2CH_3$; $E^2 = COCH_3$

Scheme 2



3 4 5 1

[a] (a) $TiCl_4$, $CH_3COCH_2CO_2Me$, pyridine, THF, 0 °C, 12 h, 75%; (b) $ClSiMe_3$, CuCN·2LiCl (2 equiv), $Me_3SiC{\equiv}CCH_2CH_2MgCl$, THF, −78 °C, 1 h, 94%; (c) *n*-Bu_4NF, THF, 0 °C, 1 h, 94%.

The preparation of the triyne **1** was efficiently achieved in three steps from the known aldehyde **3**[3] in 66% overall yield (Scheme 2). Knoevenagel condensation[9] of **3** with methyl acetoacetate led to the unsaturated β-keto ester **4** which was converted in the 1,4-adduct **5** by using the Nakamura procedure.[10] Subsequent desilylation afforded the desired triyne **1**. Before performing this sequence in a one-pot operation, we determined the optimal conditions for each synthetic transformation. We showed that, independently, the ene type reaction, the [2 + 2 + 2] cycloaddition, and the [4 + 2] cyclization proceeded perfectly following the usual protocols[3,7] with a total chemo- and regioselectivity and as expected[8] with a high level of diastereoselectivity (86/14).[11] However, our initial attempts of the one-pot sequence did not allow the formation of the tetracyclic compound but gave untractable materials and traces amount of benzocyclobutenes in which the double bond had migrated in the thermodynamically more stable endocyclic position. This migration, already observed,[3] seems to result from a partial decomposition of the catalyst due to a too long reaction time in refluxing decane. In order to avoid this migration and to achieve the one-pot sequence, we added a strong donor ligand such as diphenylphosphinoethane (dppe) which is able to strongly associate the cobalt species.[12]

Thus, exposure of the triyne **1** to 5 mol % of $CpCo(CO)_2$ under irradiation at 80 °C for 8 h afforded the enecycloadducts **6a** and **6b**, which after subsequent addition of bis(trimethylsilyl)ethyne (btmse) provided the

(1) For Pd-catalyzed cycloisomerizations, see: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42. (b) Trost, B. M. *Janssen Chimica Acta* **1991**, *9*, 3–9. (c) Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923–1924. (d) Trost, B. M.; Shi, Y. *Ibid.* **1992**, *114*, 791–792. (e) Negishi, E.-I.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253–3256. (f) Meyer, F. E.; Henniges, H.; de Meijere, A. *Ibid.* **1992**, *33*, 8039–8042. (g) Takacs, J. M.; Zhu, J.; Chandramouli, S. *J. Am. Chem. Soc.* **1992**, *114*, 773–774. (h) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304–5306. (i) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157–160. (j) Trost, B. M.; Gelling, O. J. *Ibid.* **1993**, *34*, 8233–8236. (k) Trost, B. M.; Czeskis, B. A. *Ibid.* **1994**, *35*, 211–214.

(2) (a) For Co-catalyzed cyclizations, see: Malaska, M. J.; Vollhardt, K. P. C. In *Advances in Natural Product Chemistry*; Atta-ur-Rhaman, Ed.; Harwood Academic Publishers: New York, 1992; pp 53–63. (b) For Rh-catalyzed version, see: Grigg, R.; Scott, R.; Stevenson, R. *J. Chem. Soc., Perkin Trans 1* **1988**, 1357–1364. (c) For Fe-catalyzed version, see: Takacs, J. M.; Weidner, J. J.; Takacs, B. E. *Tetrahedron Lett.* **1993**, *34*, 6219–6222. (d) For Zr-catalyzed version, see: Agnel, G.; Negishi, E.-I. *J. Am. Chem. Soc.* **1991**, *113*, 7424–7426.

(3) Aubert, C.; Gotteland, J. P.; Malacria, M. *J. Org. Chem.* **1993**, *58*, 4298–4305. *Chemtracts-Org. Chem.* **1993**, 332–335.

(4) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1–20.

(5) Vollhardt, K. P. C. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 534–556.

(6) For an excellent review dealing with the growing field of the cascade chemistry, see: Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163.

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(8) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677–6680.

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(10) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025–4028 and 4029–4032.

(11) The two diastereomers **6a** and **6b** were unseparable, and the diastereoselectivity (86/14) was determined on the crude mixture by ^{1}H-NMR.

(12) Butenschön, H.; Kettenbach, R. T.; Krüger, C. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1066–1068.

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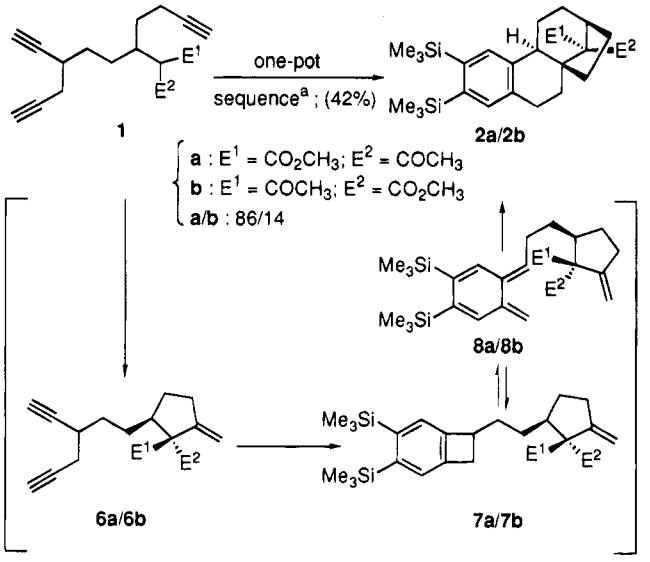
Scheme 3



[a] Reaction conditions: (i) 5% $CpCo(CO)_2$, hν, 80 °C, 8 h; (ii) btmse, 136 °C, hν, 15 min; (iii) 5% dppe, decane, 175 °C, 12 h.

benzocyclobutenes **7a** and **7b** (each synthetic individual transformation was evidenced by TLC). After 5 mol % of dppe was added, the reaction mixture was heated in refluxing decane for 12 h and we were pleased to observe the formation of a 86/14 mixture[13] of tetracyclic compounds **2a** and **2b** in 42% overall isolated yield[14] (Scheme 3).

The structure of **2a** and **2b** was fully elucidated by high field NMR analyses establishing a *trans* B/C ring junction configuration characteristic of the phyllocladane skeleton.[15] The assigned stereochemistry of **2a** was unambiguously confirmed by a X-ray crystallography.[16]

The formation of the phyllocladane framework was the result of a total stereoselectivity during the intramolecular Diels–Alder reaction through the transition state **8A** *versus* **8B** (Scheme 4). Indeed, a severe H_1–H_{12} nonbonding interaction, as we reported earlier,[3] with an additional destabilizing steric hindrance between the bulky *gem*-dicarbonyl substituent and the *o*-quinodimethane were developed for the latter.

In summary, this one-pot sequence of cyclizations allowed the formation of six carbon–carbon bonds with a total regio- and chemoselectivity and with a high level of diastereoselectivity.[17] This concise strategy can be viewed as an illustration of the very high performance of cobalt(I) catalyses to the synthesis of complex polycyclic molecules.

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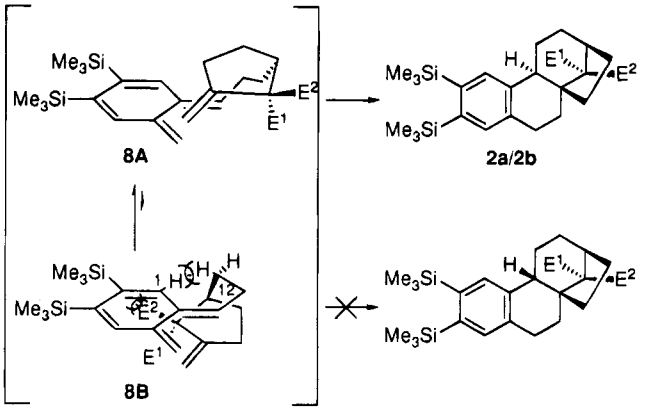
Scheme 4



Supplementary Material Available: ^1H and ^{13}C-NMR spectra for **1**, **6**, **2a**, **2b** (8 pages).

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(13) The ratio of the tetracyclic compounds **2a** and **2b** resulted from the diastereoselectivity of the initial ene type reaction (**6a/6b** = 86/14). Finally, the total stereoselective intramolecular Diels–Alder reaction led to **2a** and **2b** which are epimers at the β-keto ester position.

(14) A 42% overall isolated yield means that each synthetic individual transformation is performed in 75% average yield.

(15) Typical procedure for the preparation of **2a** and **2b**: the reactions were carried out under argon in a flame-dried flask and all the solutions were degassed by three freeze-pump-thaw cycles. Each synthetic individual transformation was evidenced by TLC. $CpCo(CO)_2$ (7 μL; 5.8×10^{-2} mmol) was added in boiling solution of **1** (230 mg, 0.5 mmol) in benzene (4 mL) and was irradiated (using a projector lamp: ELW, 300 W, 50% of its power). After 8 h, warm bis(trimethylsilyl)ethyne (8.5 mL) was quickly added. After the mixture was refluxed and irradiated for an additionnal 30 min, a solution of diphenylphosphinoethane (60 mg, 0.15 mmol) in decane (50 mL) was added. After being heated at reflux for 12 h, the solvents were removed by vacuum transfer. The crude residue was purified by flash chromatography to afford the tetracyclic compounds **2a** and **2b** in 42% yield (**2a**: 82 mg, 86%; **2b**: 16 mg, 14%). **2a**: ^1H NMR (400 MHz, C_6D_6) δ = 7.74 (s, 1H); 7.54 (s, 1H); 3.46 (dd, *J* = 10.4, 5.5 Hz, 1H); 3.27 (s, 3H); 2.76 (ddd, *J* = 12.6, 5.5, 4.9 Hz, 1H); 2.71–2.67 (m, 1H); 2.43 (dt, *J* = 12.6, 5.5 Hz, 1H); 2.29 (ddd, *J* = 12.1, 6.0, 5.5 Hz, 1H); 2.27 (m, 1H); 2.22 (m, 1H); 2.16 (ddd, *J* = 12.6, 5.5, 2.2 Hz, 1H); 2.20 (m, 1H); 1.96 (s, 3H); 1.82 (dt, *J* = 12.1, 4.9 Hz, 1H); 1.60 (ddd, *J* = 9.3, 4.4, 4.4 Hz, 1H); 1.47 (m, 1H); 1.46 (m, 1H); 1.22 (ddd, *J* = 9.9, 4.9, 4.9 Hz, 1H); 0.47 (s, 9H); 0.46 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6) δ = 202.9; 172.2; 142.6; 142.1; 139.5; 136.5; 135.8; 134.7; 74.8; 51,2; 48.9; 42.0; 40.9; 29.4; 29.3; 29.2; 28.1; 27.8; 27.0; 25.1; 2.2; 2.1. **2b**: ^1H NMR (400 MHz, C_6D_6) δ = 7.73 (s, 1H); 7.54 (s, 1H); 4.10 (dd, *J* = 11.5, 5.7 Hz, 1H); 3.25 (s, 3H); 2.74–2.66 (m, 1H); 2.72–2.55 (m, 1H); 2.63–2.60 (m, 2H); 2.35–2.23 (m, 1H); 1.93 (s, 3H); 1.68–1.60 (m, 3H); 1.55–1.48 (m, 1H); 1.48–1.38 (m, 1H); 1.38–1.29 (m, 1H); 1.31–1.24 (m, 2H); 0.5 (s, 9H); 0.48 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6) δ = 202.8; 171.1; 142.8; 141.8; 139.9; 136.5; 135.4; 134.5; 73.7; 51.3; 49.0; 42.0; 38.3; 30.6; 30.2; 30.1; 28.9; 27.7; 26.7; 24.8; 2.3; 2.1. **2a** + **2b**: IR (neat) ν = 3010; 2940; 2395; 1730; 1700; 1430; 1250; 1210; 850; 830 cm^{-1}. MS *m*/*z* (%): 456 (60) [M^+], 441 (23), 409 (4), 381 (7), 353 (100), 340 (8), 309 (9), 301 (15), 265 (14), 237 (10), 213 (13), 197 (9), 161 (7), 147 (12), 131 (23). Anal. Calcd for $C_{26}H_{40}O_3Si_2$: C, 68.37; H, 8.83. Found: C, 68.72; H, 9.08.

(16) The authors have deposited atomic coordinates for **2a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Cristallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, UK.

(17) It is noteworthy that the absolute stereochemistry of the tetracyclic compound is directly associated with the control of the stereogenic center created during the 1,4-addition. Indeed, we are currently investigating the enantioselective 1,4-addition.