Reactions of Bis(silyl enol ether)s

[3+3] Cyclizations of 1,3-Bis(silyl enol ether)s with 1,1-Diacetylcyclopentane and 1,1-Diacetylcyclopropane**

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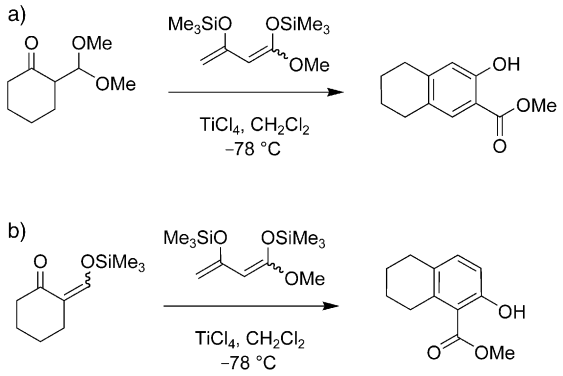
Domino reactions facilitate the rapid assembly of complex products in a one-pot process.[1] Despite the simplicity of the idea, domino cyclizations of 1,3-dicarbonyl dianions[2] with dielectrophiles are relatively rare.[3] As a result of their high negative charge density, ambident dianions are very reactive compounds, and many side reactions can occur, such as polymerization, decomposition, deprotonation, formation of open-chain products, elimination, and single-electron-transfer processes. A number of base-mediated cyclization reactions of activated (symmetrical) 1,3,5-tricarbonyl compounds (e.g. diethyl acetone-1,3-dicarboxylate) with enolizable 1,3-dicarbonyl derivatives have been reported.[4] In contrast, many side reactions, such as deprotonation or reduction of the dielectrophile, can interfere with the direct cyclization of (unsymmetrical) 1,3-dicarbonyl dianions with enolizable and non-enolizable 1,3-diketones.[5] A solution to this problem was developed by Chan and co-workers. They reported the synthesis of benzene derivatives and salicylic acid esters by the Lewis acid mediated cyclization of acetals of β,β-ketoaldehydes, β-ketocarboxylic acid esters, and β-ketocarboxylic acid chlorides (Scheme 1a), and of 3-silyloxyalk-2-en-1-ones (Scheme 1b) with 1,3-bis(silyl enol ether)s. 1,3-Bis-



Scheme 1. Cyclizations of 1,3-bis(silyl enol ether)s reported by Chan et al.[6b,8]

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(silyl enol ether)s can be regarded as electroneutral 1,3-dicarbonyl dianion equivalents.[6–8]

Herein, we report the first cyclizations, to the best of our knowledge, of 1,3-bis(silyl enol ether)s with 1,1-diacetylcyclopentane and 1,1-diacetylcyclopropane. The reaction of 1,3-bis(silyl enol ether)s with 1,1-diacetylcyclopentane afforded spiro[5.4]cyclodecenones, which underwent a domino rearrangement upon treatment with trifluoroacetic acid (TFA). This transformation provided efficient access to functionalized bicyclo[4.4.0]deca-1,4-dien-3-ones with an angular methyl group. The products are of considerable pharmacological relevance and represent useful precursors for the synthesis of steroids (e.g. corticoids) and terpene analogues.[9] Furthermore, we report a novel [3+3] cyclization of 1,3-bis(silyl enol ether)s with 1,1-diacetylcyclopropane, which allows an efficient one-pot synthesis of salicylates that contain a halogenated side chain. The strategic placement of the latent functionality in these products makes them versatile intermediates for the synthesis of natural product analogues and electron-rich styrenes.[10]

The $TiCl_4$-mediated cyclization of the bis(silyl enol ether) **1a** ($R^1 = H$, $R^2 = OEt$) with 1,1-diacetylcyclopentane (**2a**)[11] afforded the spiroannulated 3-hydroxycyclohex-5-en-1-one **3a** in good yield (Scheme 2). The choice of Lewis acid, the temperature (−78→20 °C), and the presence of molecular sieves (4 Å) proved to be important parameters in the optimization of this reaction. The reaction of **3a** with TFA gave **5a** in high yield. The structure of **5a** was established by NMR spectroscopy (coupling constants, H,H COSY) and was independently confirmed by X-ray crystal-structure analysis (Figure 1).[12] The saturated six-membered ring has a distorted chair conformation; the cyclohexadienone moiety is slightly distorted from planarity. The formation of **5a** can be explained by an acid-catalyzed Wagner–Meerwein rearrangement (Scheme 2).[13] The intermediacy of the spiro compound **4** is supported by the fact that **4** could be isolated when the reaction was stopped after just 3 h. The structurally related isomer **6** was not isolated from the reaction mixture.

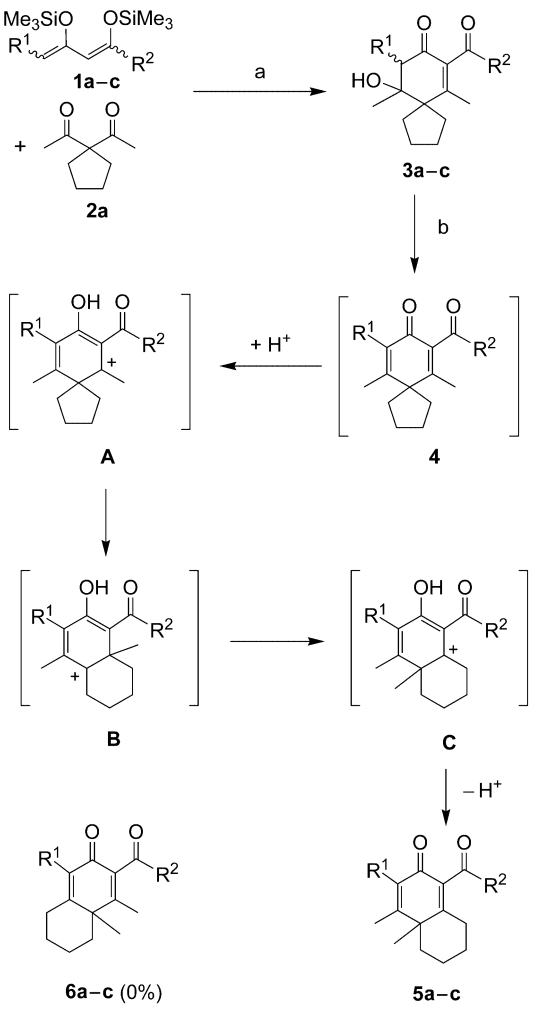
The 1,3-bis(silyl enol ether)s **1b** and **1c**, derived from acetylacetone and ethyl 3-oxohexanoate, respectively, were also used successfully as starting materials. The reaction of **2a** with **1b** and **1c** gave the spiro compounds **3b** and **3c**, which were transformed into the bicyclo[4.4.0]deca-1,4-dien-3-ones **5b** and **5c** in the presence of TFA (Table 1).

The reaction of the bis(silyl enol ether)s **1a** and **1b** with 2,2-diacetylindane (**2b**) afforded the spiro compounds **3d** and **3e**, respectively, in good yields (Scheme 3). Treatment of **3d** and **3e** with TFA afforded the interesting tricyclic products **5d** and **5e**, respectively, which can be regarded as 9,9a-dihydroanthracenes. The products were formed via inter-

Table 1: Synthesis of **3a–c** and **5a–c**.

Entry	R^1	R^2	Yields [%][a]	
			3	**5**
a	H	OEt	78	97
b	H	Me	67	95
c	Et	OEt	41[b]	88

[a] Yields of isolated products. [b] Diastereomeric mixture (4:1, assignment unclear).



Scheme 2. Cyclizations of 1,3-bis(silyl enol ether)s **1** with 1,1-diacetylcyclopentane (**2a**); a) 1. $TiCl_4$ (2.0 equiv), CH_2Cl_2, molecular sieves (4 Å), −78→20 °C, 2. H^+, H_2O; b) TFA, CH_2Cl_2, 72 h.

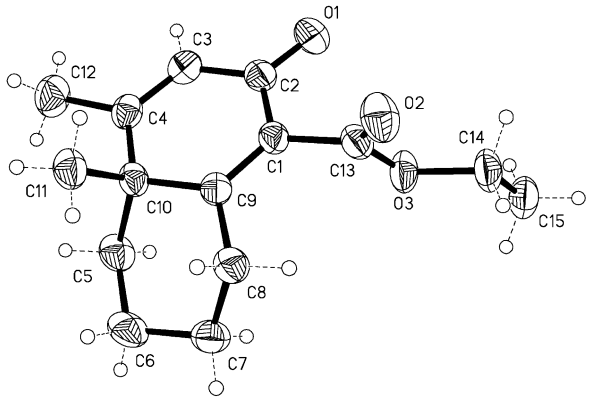
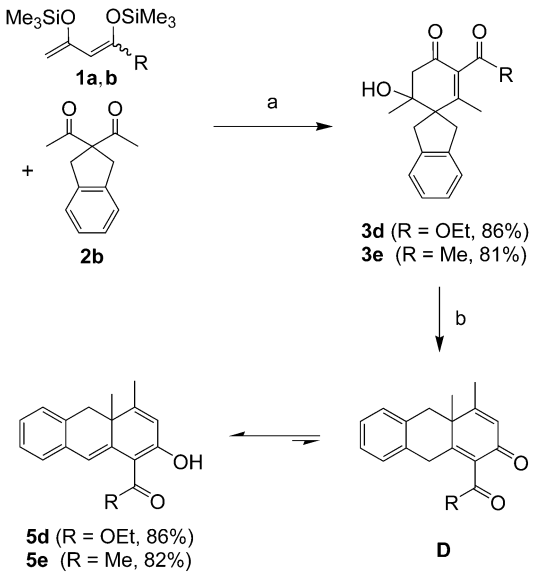


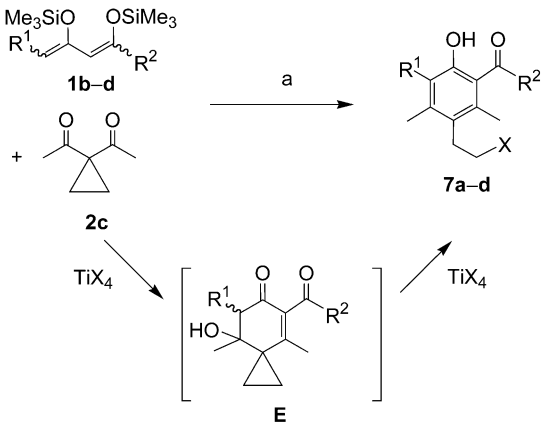
Figure 1. ORTEP plot of **5a**. Non-hydrogen atoms are represented by thermal ellipsoids of 50% probability. Selected bond lengths [Å] and angles [°]: O1-C2 1.227(2), C1-C9 1.345(2), C1-C2 1.473(2), C3-C4 1.335(3), C4-C10 1.509(2), C5-C6 1.520(3), C6-C7 1.517(3), C7-C8 1.532(2); C9-C1-C2 122.16(15), C1-C2-C3 122.52(17), C4-C3-C2 123.21(17), C6-C5-C10 113.67(14), C6-C7-C8 110.96(15).



Scheme 3. Cyclizations of 1,3-bis(silyl enol ether)s **1** with 2,2-diacetylindane (**2b**); a) 1. $TiCl_4$ (2.0 equiv), CH_2Cl_2, molecular sieves (4 Å), −78→20 °C, 2. H^+, H_2O; b) TFA, CH_2Cl_2, 72 h.

mediate **D** and reside in the thermodynamically more stable enol tautomeric form as a result of conjugation of the enol with the aryl ring.

An unexpected cyclization was observed in the reaction of the silyl enol ether **1d** with 1,1-diacetylcyclopropane (**2c**)[11] in the presence of $TiCl_4$ (Scheme 4).[14] The functionalized salicylic ester **7a**, which contains a chloro-substituted side



Scheme 4. Cyclizations of 1,3-bis(silyl enol ether)s **1** with 1,1-diacetylcyclopropane (**2c**); a) 1. TiX_4 (X = Cl, Br; 2.0 equiv), CH_2Cl_2, molecular sieves (4 Å), −78→20 °C, 2. H^+, H_2O.

chain, was isolated in 82 % yield. The use of $TiBr_4$ (in place of $TiCl_4$) resulted in the formation of the bromo-substituted salicylate **7b** in 80 % yield (Table 2).

The formation of **7a** can be explained by a $TiCl_4$-mediated cyclization with formation of the intermediate **E**. A subsequent $TiCl_4$-mediated cyclopropylcarbinyl→homoallyl rearrangement[14] and elimination of water afforded product **7a**.

Table 2: Synthesis of **7a–d**.

1	7	X	R^1	R^2	Yield of **7** [%][a]
d	**a**	Cl	H	OMe	82
d	**b**	Br	H	OMe	80
b	**c**	Cl	H	Me	68
c	**d**	Cl	Et	OEt	40

[a] Yields of isolated products.

The spiro[5.2]cyclooctenone **E** could be isolated in up to 55 % yield when only a small amount of $TiCl_4$ (0.5–0.7 equiv) was used. The use of larger quantities of the Lewis acid resulted in the formation of significant amounts of **7a**. The reaction of **2c** with the bis(silyl enol ether)s **1b** and **1c** afforded the functionalized salicylates **7c** and **7d** in good yields (Table 2). Further studies related to the scope and limitations of the cyclization reactions presented herein and their application in organic synthesis are in progress.

Experimental Section

Typical procedure for **3**: **3a**: $TiCl_4$ (0.22 mL, 2.0 mmol) was added dropwise at −78 °C under an argon atmosphere to a stirred solution of **2a** (0.154 g, 1.0 mmol) and **1a** (0.415 g, 1.5 mmol) in CH_2Cl_2 (100 mL) in the presence of molecular sieves (4 Å; 1.0 g). The reaction mixture was allowed to warm to 20 °C over 6 h, was stirred for an additional 6 h at 20 °C, and was then filtered. The filtrate was poured into an aqueous solution of HCl (10 %, 100 mL). The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexane/ethyl acetate 3:2) to give **3a** (0.208 g, 78 %) as colorless crystals; m.p. 107–108 °C; $R_f = 0.35$ (hexane/ethyl acetate 1:1); IR (KBr): $\tilde{\nu} = 3410$ s, 2966 s, 1724 s, 1663 s, 1619 s, 1470 m, 1385 s, 1342 s, 1237 s, 1205 s, 1089 s, 1026 cm^{-1} m; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 4.29$ (q, 2H, $J = 7.2$ Hz; OCH_2), 2.64 (br, 2H; CH_2), 2.16 (br, 2H; CH_2), 1.98 (s, 3H; CH_3), 1.88 (br, 1H; OH), 1.76 (brs, 6H; CH_2), 1.32 (t, 3H, $J = 7.2$ Hz; CH_3), 1.26 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 194.2$, 167.5, 164.6, 131.7 (C), 75.7 (C-OH), 61.5 (CH_2), 56.4 (C), 50.0, 33.5, 33.5, 28.5, 28.5 (CH_2), 25.1, 18.0, 14.4 ppm (CH_3); MS (EI, 70 eV): *m*/*z* (%): 266 (M^+, 9), 220 (52), 162 (100); elemental analysis: calcd for $C_{15}H_{22}O_4$: C 67.64, H 8.32; found: C 67.38, H 8.45. All compounds were characterized by spectroscopic methods and gave correct elemental analyses and/or high-resolution mass spectra.

Typical procedure for **5**: **5a**: TFA (0.4 mL, 5.2 mmol) was added dropwise at 20 °C to a stirred solution of **3a** (0.134 g, 0.5 mmol) in CH_2Cl_2 (0.4 mL) and the mixture was stirred until all the starting material had disappeared (72 h; monitored by TLC). The solvent and TFA were then removed in vacuo, and the residue was purified by column chromatography (silica gel; hexane/ethyl acetate 3:2) to give **5a** (0.120 g, 96 %) as colorless crystals; m.p. 79–80 °C; $R_f = 0.30$ (hexane/ethyl acetate 3:2); IR (KBr): $\tilde{\nu} = 2941$ s, 1730 s, 1658 s, 1630 m, 1447 m, 1390 m, 1324 w, 1265 s, 1245 s, 1050 cm^{-1} m; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.14$ (q, 1H, $^4J = 1.2$ Hz; C=CH), 4.33 (q, 2H, $J = 7.2$ Hz; OCH_2), 2.47–2.41 (m, 2H; CH_2), 2.12–1.98 (m, 2H; CH_2), 2.01 (d, 3H, $^4J = 1.2$ Hz; CH_3), 1.78–1.71 (m, 2H; CH_2), 1.44–1.37 (m, 2H; CH_2), 1.36 (s, 3H; CH_3), 1.34 ppm (t, 3H $J = 7.2$ Hz; CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 182.0$, 167.2, 166.0, 163.8, 131.1 (C), 126.3 (CH), 61.3 (CH_2), 43.2 (C), 37.6, 29.8, 28.1 (CH_2), 22.6 (CH_3), 21.2 (CH_2), 19.0, 14.2 ppm (CH_3); MS (EI, 70 eV): *m*/*z* (%): 248 (M^+, 71), 233 (46), 203 (72), 178 (100); elemental analysis: calcd for $C_{15}H_{20}O_3$: C 72.55, H 8.11; found: C 72.59, H 8.39.

Typical procedure for **7**: **7a**: Compound **2c** (0.136 g, 1.1 mmol) was treated with **1d** (0.421 g, 1.6 mmol) in the presence of $TiCl_4$ (0.22 mL, 2.0 mmol), as described for the synthesis of **3**. Chromatography: silica gel; hexane/ethyl acetate 4:1. Compound **7a** (0.251 g, 82%) was obtained as colorless crystals; m.p. 73–74 °C; $R_f = 0.53$ (hexane/ethyl acetate 4:1); IR (KBr): $\tilde{\nu} = 3026$ m, 2906 s, 1657 s, 1601 m, 1574 m, 1468 m, 1437 s, 1355 s, 1239 s, 1151 m, 1072 m, 804 cm^{-1} s; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 10.68$ (s, 1H; OH), 6.70 (s, 1H; ArH), 3.95 (s, 3H; OCH_3), 3.51–3.46 (m, 2H; CH_2Cl), 3.12–3.06 (m, 2H; CH_2), 2.48 (s, 3H; CH_3), 2.32 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.8$, 160.3, 144.2, 139.0, 127.1, 117.2, 111.9, 52.1, 42.2, 33.0, 21.0, 18.5 ppm; MS (EI, 70 eV): *m/z* (%): 244.5 ([*M*+2]$^+$, 15), 242.5 (M^+, 47), 212.5 (41), 210.4 (93), 161.4 (100); elemental analysis: calcd for $C_{12}H_{15}O_3Cl$: C 59.39, H 6.22; found: C 59.56 H 6.50.

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[1] L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131.
[2] L. Weiler, *J. Am. Chem. Soc.* **1970**, *92*, 6702.
[3] P. Langer, *Chem. Eur. J.* **2001**, *7*, 3858.
[4] a) V. Prelog, J. Würsch, K. Königsbacher, *Helv. Chim. Acta* **1951**, *34*, 258; b) M. Beringer, I. Kuntz, *J. Am. Chem. Soc.* **1951**, *73*, 364; c) S. H. Bertz, G. Dabbagh, *Angew. Chem.* **1982**, *94*, 317; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 306; for intramolecular reactions of unsymmetrical derivatives, see: d) M. Yamaguchi, K. Hasebe, T. Minabi, *Tetrahedron Lett.* **1986**, *27*, 2401; e) S. G. Gilbreath, C. M. Harris, T. M. Harris, *J. Am. Chem. Soc.* **1988**, *110*, 6172.
[5] For the cyclization of a 1,3-dicarbonyl dianion with 3-(*N,N*-dimethylamino)-2-ethylacrolein, see: D. H. R. Barton, G. Dressaire, B. J. Willis, A. G. M. Barrett, M. Pfeffer, *J. Chem. Soc. Perkin Trans. 1* **1982**, 665.
[6] a) T.-H. Chan, P. Brownbridge, *J. Chem. Soc. Chem. Commun.* **1979**, 578; b) T.-H. Chan, P. Brownbridge, *J. Am. Chem. Soc.* **1980**, *102*, 3534; c) G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115*, 830.
[7] Review: P. Langer, *Synthesis* **2002**, 441.
[8] a) T. H. Chan, T. Chaly, *Tetrahedron Lett.* **1982**, *23*, 2935; b) P. Brownbridge, T.-H. Chan, M. A. Brook, G. J. Kang, *Can. J. Chem.* **1983**, *61*, 688.
[9] a) N. Ezaki, T. Shomura, M. Koyama, T. Niwa, M. Kojima, S. Inouye, T. Niida, *J. Antibiot.* **1981**, *34*, 1363; b) M. Kaneda, S. Nakamura, N. Ezaki, Y. Iitaka, *J. Antibiot.* **1981**, *34*, 1366; c) N. Ezaki, M. Koyama, T. Shomura, T. Tsuruoka, S. Inouye, *J. Antibiot.* **1983**, *36*, 1263; d) G. T. Carter, J. A. Nietsche, J. J. Goodman, M. J. Torrey, T. S. Dunne, M. M. Siegel, D. B. Borders, *J. Chem. Soc. Chem. Commun.* **1989**, 1271.
[10] *Römpp Lexikon Naturstoffe* (Eds.: B. Fugmann, S. Lane-Fugmann, W. Steglich), Thieme, Stuttgart, **1997**.
[11] The starting materials were prepared according to known procedures: a) N. S. Zefirov, S. I. Kozhushkov, T. S. Kuznetsova, R. Gleiter, M. Eckert-Maksic, *J. Org. Chem. USSR (Engl. Transl.)* **1986**, 95; b) O. Itoh, N. Iwakoshi, T. Saitoh, H. Katano, Y. Fujisawa, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 177; c) W. Adam, T. Heidenfelder, C. Sahin, *Synthesis* **1995**, 1163; d) K. Beck, S. Hünig, *Chem. Ber.* **1987**, *120*, 477.
[12] CCDC 211439 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
[13] For acid-mediated dienone–phenol rearrangements, see: B. Hagenbruch, S. Hünig, *Chem. Ber.* **1983**, *116*, 3884.
[14] "Carbocyclic Three-Membered Ring Compounds": *Methods Org. Chem.* (Houben-Weyl) 4th ed. 1952–, *Vol. E17*, **1996**.

