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Tetrahedron Letters 48 (2007) 8234–8237
Tetrahedron Letters

A new access to ring-fused cyclopropanols through samarium diiodide-induced 3-*exo*-trig-cyclisations

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Received 5 July 2007; revised 6 September 2007; accepted 11 September 2007
Available online 15 September 2007

Abstract—Benzobicyclic δ-oxo-α,β-unsaturated esters easily prepared from tetralones or benzosuberone, readily cyclise in the presence of samarium diiodide and *tert*-butanol according to a totally *syn* mode, leading selectively to 'cis' ring-fused cyclopropanols that spontaneously lactonise to tetracyclic compounds.

In previous publications,[1,2] we reported that *acyclic* δ-oxo-α,β-unsaturated esters and δ-oxo-alkylidenemalonates readily cyclise to cyclopropane compounds in the presence of 2 equiv of samarium diiodide[3] and a proton source such as *tert*-butanol or phenol in THF.[4] These 3-*exo*-trig-cyclisations most probably occur at a radical stage. They may involve either addition of the radical anion formed by monoelectronic reduction of the enoate moiety onto the carbonyl group or more likely, as represented in Figure 1, addition of the ketyl radical onto the electron poor ethylenic bond. Depending on the substrate and the exact conditions of the reaction, they may take place either in an *anti* or in a *syn* fashion and therefore give either '*trans*' cyclopropanols or '*cis*' cyclopropanols (Fig. 1). '*cis*' Cyclopropanols usually react further in situ to give the corresponding lactones.[1]

We report here an extension of our studies to cyclic substrates. Indeed, such substrates should give access to ring-fused cyclopropanols that are important synthetic intermediates, for instance as regards ring expansion reactions.[5] Ring-fused cyclopropanols are also encountered as substructures of natural compounds such as phorbol–isophorbol.[6]

We have studied the cyclisation of δ-oxo-α,β-unsaturated esters derived from cyclohexanone **1**, diversely substituted tetralones **2*i*** (with i = a, b or c depending on the substitution pattern of the aromatic ring), 1-benzosuberone **3** and 4-chromanone **4** (Fig. 2).

All these compounds were synthesised in a straightforward way. Thus **1** was prepared by the addition of *N*-cyclohexylidene-1-phenylethylamine on to methyl propiolate.[7] Compounds **2**–**4** were obtained in three steps from cyclohexanone, tetralones, benzosuberone or 4-chromanone through: (i) conversion to the 2-hydroxymethylene derivatives (HCO_2Et, EtONa),[8]

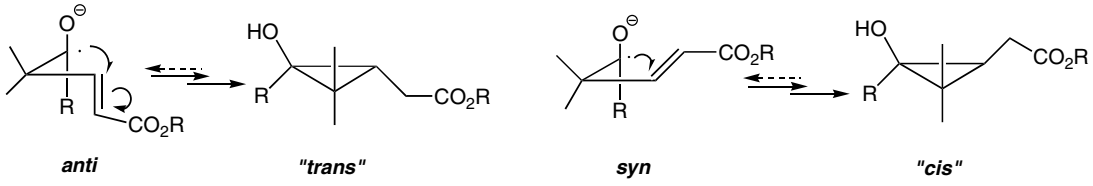

Figure 1. Stereochemistry of 3-*exo*-trig cyclisation of δ-oxo-α,β-unsaturated esters.

Keywords: Cyclisations; Cyclopropanols; Diastereoselectivity; Radicals; Samarium.
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0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.09.071

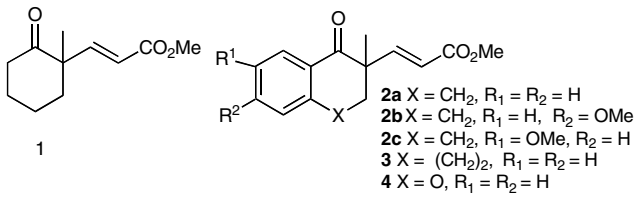


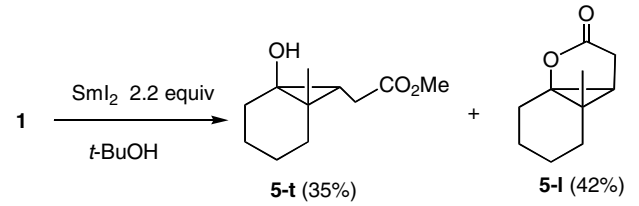
Figure 2. Cyclisation substrates.

(ii) C-methylation (MeI, TBAHS (tetrabutylammonium bisulfate)/NaOH, biphasic system CH_2Cl_2–H_2O)[9] to give α-methyl-β-ketoaldehydes, (iii) conversion of the ketoaldehydes to unsaturated monoesters **3** and **4** by Wadsworth–Emmons olefination (NaH, $(MeO)_2P(O)CH_2CO_2Me$, THF, 0 °C).[10]

The cyclisation reactions were performed, as already described,[1,2] in degassed THF under an argon atmosphere and using *tert*-butanol as the proton donor.[11] Reactions were usually complete within 2–3 h (by TLC). After work-up, the products were separated by column chromatography on silica gel and their structures were determined by spectroscopy, including NMR NOE experiments when necessary.

The results of the cyclisation reactions are reported in Scheme 1 and Table 1.

The results obtained with the cyclohexane-derived δ-oxo-α,β-unsaturated ester **1** parallel those obtained in the acyclic series when R at δ position is an alkyl group.[1] The cyclisation takes place with a very low diastereoselectivity and leads to an almost equimolecular mixture of *trans* cyclopropanol **5-t** and lactone **5-l** derived from the cis isomer.



Scheme 1. SmI_2-mediated cyclisation of cyclohexanone-derived δ-oxo-α,β-unsaturated ester **1**.

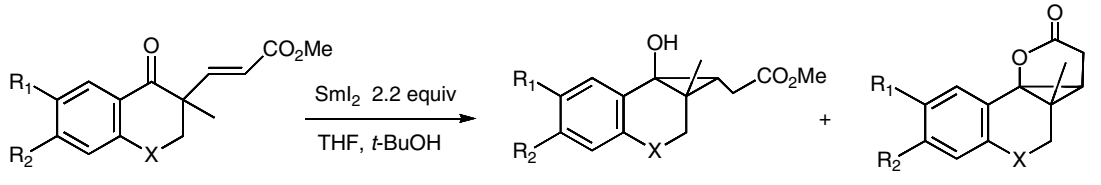
Monoesters of the benzobicyclo series (Table 1) behave very differently. Indeed, if we except the 4-chromanone derivative **4**, all conjugated esters of Table 1 stereoselectively cyclise to lactones **6-l** or **7-l** (*syn* selectivity). This *syn* selectivity strikingly differs from that observed with acyclic compounds with arylic δ-group (phenyl, 2-furyl, 2-thienyl). Indeed, those compounds exhibit marked *anti* selectivity (85–100%).[1]

The strong bias towards *syn* cyclisation exhibited by the benzobicyclo structure is, at the present time, not clearly understood. The potentially reversible character of 3-*exo*-trig-cyclisations complicates the analysis of the reaction. On steric grounds, an *exo* orientation of the carbomethoxymethyl group in fused-ring cyclopropanols is certainly favoured but this can hardly account for a 100% *syn* selectivity. If we assume that the cyclisation processes are not reversible *in the conditions of our reactions* (due to fast subsequent protonation for instance), a possibility is that, owing to its quite rigid structure, the benzobicyclo structure induces subtle conformational constraints in the transition state that could affect the stereoselectivity of the reaction. But the nature of these constraints remains obscure.

Total *syn* selectivity might also point out to a chelating effect of samarium. However, since aromatic ketones are more easily reduced than crotonate esters,[12] the reaction is more likely to involve addition of the ketyl radical to the enoate moiety rather than addition to the carbonyl of the radical anion issued from reduction of the enoate moiety. If so, owing to the *E* configuration of the ethylenic bond, it is difficult to invoke a chelation effect except if the transition state is late.

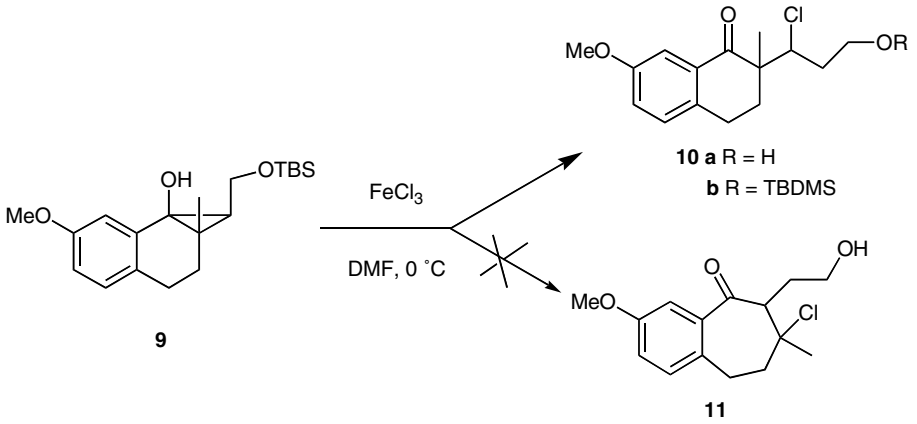
Attempts to achieve, in the presence of $FeCl_3$ radical ring expansion reactions from fused ring cyclopropanols obtained either directly from SmI_2-induced cyclisations or after reduction of the lactones, were unsuccessful. Indeed, in our case, radical fragmentation occurs at the external C–C bond and not at the C–C bond of

Table 1. SmI_2-mediated cyclisation of benzobicyclic δ-oxo-α,β-unsaturated esters **2**–**4**



Substrates	R_1	R_2	X	Products (yields)[a]	
2a	H	H	CH_2	**6a**–**t** (0)	**6a**–**l** (93)
2b	H	OCH_3	CH_2	**6b**–**t** (0)	**6b**–**l** (62)
2c	OCH_3	H	CH_2	**6c**–**t** (0)	**6c**–**l** (78)
3	H	H	$(CH_2)_2$	**7-t** (0)	**7-l** (92)
4	H	H	O	**8-t** (38)	**8-l** (53)

[a] Isolated yields.



Scheme 2. Ring opening of fused cyclopropanol **9** in the presence of $FeCl_3$.

the ring junction. For instance, compound **9** obtained from lactone **6c–l** after reduction with $LiAlH_4$ and subsequent protection of the primary alcohol function upon exposure to $FeCl_3$ led to chloro derivative **10a** (**10b** was obtained when the reaction was carried out in the presence of triethylamine) instead of the desired seven-membered chloroketone **11** (Scheme 2). To the best of our knowledge, all hitherto reported ring expansions of fused cyclopropanols involve cyclopropane substrates with an unsubstituted exocyclic carbon atom. In our case, due to the presence of the alkoxycarbonylmethyl substituent at exocyclic carbon, the competition between the formation of an endocyclic tertiary carbon radical and the formation of an exocyclic secondary (instead of primary) carbon radical favours the latter one.

References and notes

1. Bezzenine-Lafollée, S.; Guibé, F.; Villar, H.; Zriba, R. *Tetrahedron* **2004**, *60*, 6931–6944.
2. Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F.; Guillerez, M.-G. *Synlett* **2005**, 2362–2366.
3. Reviews: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338; (b) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354; for other recent reviews on SmI_2 mediated reactions see: (c) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–777; (d) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751; (e) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372.
4. For another SmI_2-induced formation of cyclopropanols, based on a double cyclisation of allyloxybenzoic acid chlorides, see: Sasaki, M.; Collin, J.; Kagan, H.-B. *Tetrahedron Lett.* **1988**, *29*, 6105–6106.
5. Kulinkovitch, O. G. *Chem. Rev.* **2003**, *103*, 2597–2632 and references cited therein.
6. Matsuya, Y.; Yamamoto, N.; Mori, M.; Saito, H.; Takeuchi, M.; Ito, M.; Nemoto, H. *Bioorg. Med. Chem.* **2005**, *13*, 4383–4388.
7. Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361–4368.
8. Ainsworth, C. *Org. Synth.* **1959**, *39*, 27–29 (Collective Vol. *4*, 536–539).
9. Tsuboi, S.; Ono, T.; Takeda, A. *Heterocycles* **1986**, *24*, 2007–2014.
10. See Ref. 1 and references cited therein.
11. *General procedure for cyclisation reactions*: To a solution of 1 mmol of substrate to be cyclised and 4 mmol of *tert*-butanol in 5–6 mL of THF at 0 °C were added dropwise 22 mL (2.2 equiv) of a 0.1 M solution of SmI_2 in THF. The reaction mixture was then stirred at room temperature with monitoring by TLC or IR spectroscopy on aliquots. Reaction was usually complete within 4–12 h. After quenching with dilute aqueous HCl, the products were extracted twice with diethyl ether. The organic phases were joined and washed with a dilute aqueous solution of sodium thiosulfate. After drying ($MgSO_4$) and evaporation of ether, the residue was column chromatographied on silica gel with appropriate mixtures of ethyl acetate and heptane or cyclohexane as the eluents.
Physical and spectroscopic data for cyclisation products:
Cyclopropanol **5-t**: yield 35%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.36 (d, $J = 7.8$ Hz, 2H), 2.01–1.87 (m, 2H), 1.71–1.58 (m, 2H), 1.51–1.22 (m, 4H), 1.23 (s, 3H), 0.91 (t, $J = 7.8$ Hz, 1H), H of hydroxylic group not detected; ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.5, 59.3, 52.2, 30.3, 29.9, 29.6, 27.8, 27.3, 23.1, 22.7, 22.6; HRMS (EI): calcd for $C_{11}H_{18}O_3$, 198.1256; found, 198.1297; IR ($CHCl_3$): 1732.
Lactone **5-l**: yield 42%, oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.81 (dd, $^2J = 19.0$ Hz, $^3J = 7.3$ Hz, 1H), 2.39 (d, $^2J = 19.0$, 1H), 2.45–2.17 (m, 2H), 1.81–1.48 (m, 4H), 1.42–1.18 (m, 3H), 1.01 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.9, 70.8, 34.0, 27.18, 25.6, 24.8, 22.7, 22.4, 21.3, 13.9; HRMS (EI): calcd for $C_{10}H_{14}O_2$, 166.0994; found, 166.1007; IR ($CHCl_3$): 1772.
Lactone **6a–l**: yield 93%, solid mp: 69–70 °C (hexane–AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, $J = 7.2$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.12 (t, $J = 7.6$ Hz, 1H), 7.03 (d, $J = 7.2$ Hz, 1H), 2,89 (dd, $^2J = 19.2$ Hz, $^3J = 7.6$ Hz, 1H), 2.54 (d, $^2J = 19.2$ Hz, 1H), 2.62 (dd $J = 4.0$ Hz, $J = 5.2$ Hz, 1H), 2.42 (td $J = 12.4$ Hz, $J = 7.3$ Hz, 1H), 2.13 (d, $J = 7.6$ Hz, 1H), 2.04 (dd, $J = 13.2$ Hz, $J = 6$ Hz, 1H), 1.68 (td, $J = 17.0$ Hz, $J = 7.3$ Hz, 1H), 1.17 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.2, 134.0, 133.0, 128.2, 126.8, 126.6, 123.5, 69.6, 31.0, 28.8, 28.0, 26.4, 20.8, 12.6. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.29; H, 6.76; IR ($CHCl_3$): 1784.
Lactone **6b–l**: yield 62%; solid mp: 122–123 °C (hexane–AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (d, $J = 8.9$ Hz, 1H), 6.80 (dd, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H), 6.66 (d, $J = 2.0$ Hz, 1H), 3.79 (s, 3H), 2.98 (dd, $^2J = 19.6$ Hz, $^3J = 8.2$ Hz, 1H), 2.58 (d, $^2J = 19.6$ Hz, 1H), 2.72–2.54 (m, 1H), 2.46 (td, $J =$ ca. 13 Hz, $J =$ ca.

8 Hz, 1H), 2.09 (d, $J = 8.2$ Hz, 1H), 2.15–2.05 (m, 1H), 1.76 (td, $J = 13.3$ Hz, $J = 4.5$ Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.1, 158.5, 134.5, 125.9, 124.5, 114.1, 111.7, 69.5, 55.5, 31.0, 28.3, 28.0, 26.5, 20.6, 12.4; HRMS (electrospray): (M+Na) calcd for $C_{15}H_{16}NaO_3$, 267.1028; found, 267.0992; IR ($CHCl_3$): 1781.5.

Lactone **6c–l**: yield 78%; solid mp: 94–96 °C (hexane–AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, $J = 2.5$ Hz, 1H), 6.98 (d, $J = 8.2$ Hz, 1H), 6.72 (dd, $J = 8.2$ Hz, $J = 2.5$ Hz, 1H), 3.81 (s, 3H), 2.96 (dd, $^2J = 19.0$ Hz, $^3J = 7.6$ Hz, 1H), 2.62 (d, $^2J = 19.0$ Hz, 1H), 2.72–2.57 (m, 1H), 2.41 (td, $J = 14.1$ Hz, $J = 6.5$ Hz, 1H), 2.20 (d, $J = 7.0$ Hz, 1H), 2.10–2.06 (dd, $J = 13.0$ Hz, $J = 6.5$ Hz, 1H), 1.72 (td, $J = 14.0$ Hz, $J = 5.0$ Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 158.7, 135.0, 129.1, 124.8, 112.6, 108.4, 69.6, 30.9, 28.7, 28.2, 25.4, 20.8, 12.5; HRMS (electrospray): (M+Na) calcd for $C_{15}H_{16}NaO_3$, 267.1009; found, 267.0992; IR ($CHCl_3$): 1784.

Lactone **7-l**: yield 92%; oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, $J = 7.0$ Hz, 1H), 7.30 (t, $J = 7.0$ Hz, 2H), 7.16 (d, $J = 7.0$ Hz, 1H), 3.13–2.98 (m, 1H), 3.07 (dd, $^2J = 19.0$ Hz, $^3J = 7.5$ Hz, 1H), 2.64 (d, $^2J = 19.0$ Hz, 1H), 2.71–2.56 (m,1H), 2.15–1.96 (m, 1H), 1.89 (dd, $J = 14.5$ Hz, $J = 6.0$ Hz, 1H), 1.62–1.52 (m, 1H), 1.47 (d, $J = 7.6$ Hz, 1H), 1.15 (s, 3H), 0.54 (td, $J = 14.0$ Hz, $J = 6.0$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.5, 140.5, 134.5, 130.9, 129.7, 129.1, 127.1, 71.5, 32.4, 31.1, 30.3, 26.5, 26.1, 22.7, 9.2; HRMS (EI): calcd for $C_{15}H_{16}O_2$, 228.2902; found, 228.2908. IR ($CHCl_3$): 1777.

Cyclopropanol **8-t**: yield 53%; solid mp: 80–81 °C (hexane–AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50 (dd, $J = 7.8$ Hz, $J = 1.0$ Hz, 1H), 7.14 (td, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 7.01 (td, $J = 7.7$ Hz, $J = 1.0$ Hz, 1H), 6.80 (dd, $J = 8.0$ Hz, $J = 1$ Hz, 1H), 4.24 (d, $J = 10.7$ Hz, 1H), 3.78 (d, $J = 10.7$ Hz, 1H), 3.62 (s, 3H), 2.37 (dd, $J = 7.3$ Hz, $J = 2.1$ Hz, 2H); 1.63 (t, $J = 7.3$ Hz, 1H), 1.33 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.1, 151.1, 126.1, 125.9, 122.0, 117.1, 66.8, 58.0, 51.9, 33.5, 32.0, 29.0, 15.1; HRMS (EI): calcd for $C_{14}H_{16}O_4$, 248.1037; found, 248.1043. IR ($CHCl_3$): 1732.

Lactone **8-l** yield 38%; solid mp: 84–86 °C (hexane–AcOEt). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (dd, $J = 7.5$ Hz, $J = 1.3$ Hz, 1H), 7.15 (td, $J = 7.5$ Hz, $J = 1.9$ Hz, 1H), 7.05 (td, $J = 7.5$ Hz, $J = 1.3$ Hz, 1H), 6.89 (d, $J = 7.5$ Hz, 1H), 4.20 (d, $J = 10.7$ Hz, 1H), 3.74 (d, $J = 10.7$ Hz, 1H), 3.05 (dd, $^2J = 19.0$ Hz, $^3J = 7.6$ Hz, 1H), 2.65 (d, $^2J = 19.0$ Hz, 1H), 2.36 (d, J=7.6 Hz, 1H), 1.18 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.5, 151.6, 127.8, 123.7, 123.6, 122.6, 117.2, 68.5, 66.2, 32.9, 30.5, 22.5, 7.5; HRMS (EI): calcd for $C_{13}H_{12}O_3$, 216.0773; found 216.0781. IR ($CHCl_3$): 1778.

12. Cammoun, C.; Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F. *Tetrahedron* **2007**, *63*, 3728–3736.