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# Triple nucleophilic additions of (trimethylsilyl)ketene acetals to tropylium derivatives: access to the core nuclei of xanthanolides

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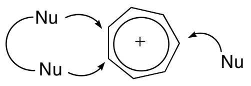
**Abstract**—The 5,7-fused system of xanthanolides was achieved in three steps from tropylium tetrafluoroborate and ketene acetals via complexes of cycloheptatriene carboxylic acid esters and chromium tricarbonyl.

The γ-butyrolactone function is very common in many natural products and confers to some interesting biological properties.[1] Among these, one can cite the 5,7-fused system found in xanthanolides, containing both a γ-lactone and a seven-membered ring, some representatives of which show surprisingly high antibacterial properties, for example xanthatin.[2]

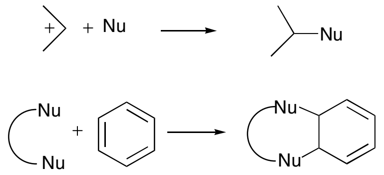
Our general interest in the synthesis of lactones involving both organic and organometallic approaches, led us to consider the general interaction of the π-nucleophiles,[3] mono- and bis(trimethylsilyl)ketene acetals, with derivatives of cycloheptatriene, in order to create, hopefully in a regioselective manner (Scheme 1), both new carbon–carbon and carbon–oxygen bonds. This approach is related to our earlier observations.



**Scheme 1.**

Indeed, in previous publications we had already demonstrated that, on the one hand, ketene acetals could be used to carry out the synthesis of polycyclic lactones via a Tsuji–Trost/palladium catalyzed allylation followed by a Herrmann/MTO (methyltrioxorhenium) catalyzed epoxidation and an intramolecular oxirane opening.[4,5] The first step here involves the interaction of the carbon nucleophile of the ketene acetal with an allylic carbocation (Scheme 2). On the other hand, the same ketene acetals were found to react, in the presence of a base, with arene (tricarbonyl) chromium complexes to give upon oxidative workup bicyclic lactones. Here, the ketene acetal behaves as a C,O dinucleophile, which adds to one of the three double bonds of the aromatic nucleus[6,7] (Scheme 2).

The purpose of this publication is to demonstrate that both types of reactions can be carried out stepwise on the same starting substrate, tropylium tetrafluoroborate, to give after triple nucleophilic addition, the 5,7-fused system containing a γ-lactone moiety. The introduction of the new functional groups was carried out in a three-step manner: (1) addition of a ketene acetal with formation of a new carbon–carbon bond, (2) coordination of the remaining triene to chromium tricarbonyl, (3)



**Scheme 2.**

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*Keywords*: Ketene acetals; Tropylium; $Cr(CO)_3$trienecomplexes; Xanthanolides.

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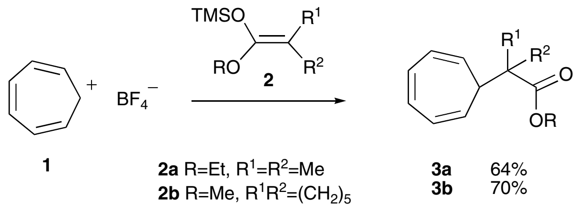


**Scheme 3.**

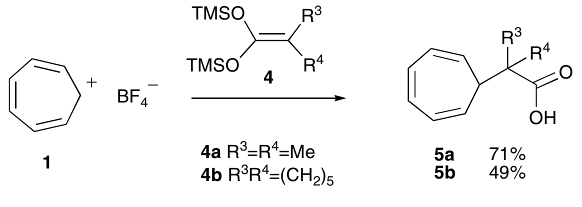
addition of a second ketene acetal leading simultaneously to the formation of a carbon–carbon and a carbon–oxygen bond[8–10] (Scheme 3).

When a dichloromethane solution of the ketene acetal **2a** was added dropwise to a suspension of tropylium tetrafluoroborate **1** in the same solvent at room temperature and left stirring for 12 h, transformation into ester **3a** (64%) was observed. Similarly, **2b** led to **3b**, which was isolated as white crystals (70%).[11]

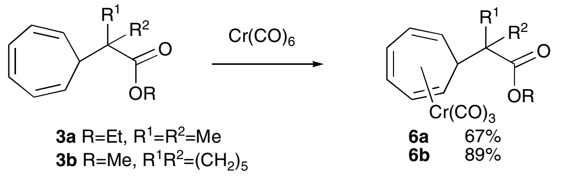
When the same reaction was carried out using **4a**, the acid **5a** was obtained as white needles (71%) along with small amounts of the corresponding less polar anhydride (4%) (Scheme 4).

Both the acid **4a** and its anhydride were characterized by their spectroscopic data and by X-ray crystallography. Similarly **4b** led to **5b**. In order to attempt the formal 1,3 addition of the 1,3-dianion of carboxylic acids originating from **4a**,**b** and *t*-BuOK, to the triene moiety of **3a**,**b**, its coordination to chromium tricarbonyl was carried out. Heating the esters in dibutyl ether in the presence of chromium hexacarbonyl led to the expected chromium (tricarbonyl) complexes **6a**,**b** as mixtures of two isomers in 67% and 89% yields, respectively (Scheme 5).

The X-ray structure of the main isomer of **6b** (bright red crystals, mp 184 °C) confirmed the *trans* orientation of the metal fragment with respect to the ester group. The final step was carried out as follows: treatment of a THF solution of complex **6a** and 2 equiv of the ketene acetal **4a** with 2 equiv of a THF solution of *t*-BuOK at −60 °C, followed by stirring of the solution at −35 °C for 4 h, cooling to −75 °C and addition of 4 equiv of iodine in THF led, after slow overnight warming to room temperature, extraction, and silica gel chromatography, to a new crystalline product **9a** (28%) along with 51% of decoordinated ester **3a**. The NMR data of **9a** were in agreement with the presence of two carbonyl groups, δ CO, 180.1 and 176.6 ppm, and of two isolated disubstituted double bonds. Moreover, a signal for a highly deshielded proton, at δ 5.18 ppm, linked to a carbon at δ 76.7 ppm confirmed the presence of the newly formed carbon–oxygen bond of the lactone.[12] Complexes **6a** and **6b** reacted similarly with **4b** to give, respectively, the lactones **9b** and **9c** in 47% yield (Scheme 6).



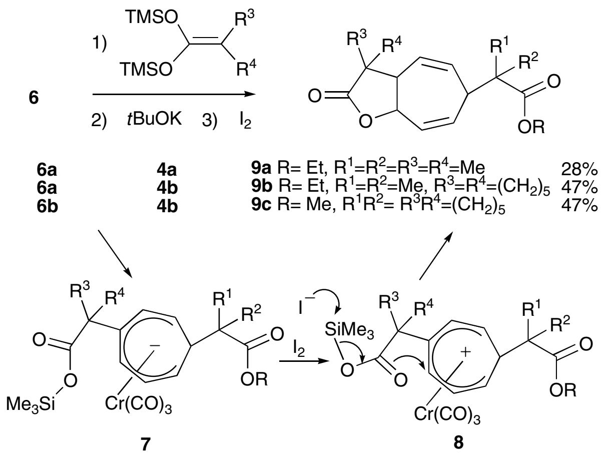
**Scheme 4.**



**Scheme 5.**

Structure **9b** was finally secured by an X-ray analysis:[12]

Figure 1 depicts a molecular view of this tricyclic compound and confirms the 'internal' γ,δ-addition of the 1,3-dianion to a double bond of the coordinated triene probably via **7** and **8** to give the desired product. According to these results, it appears clearly that the course of the second reaction (**6a** → **7**) is highly dependent on the structure of the starting complexes: since the addition of the nucleophile takes place *anti* to the metal in **6a**,**b**, the site of attack is likely to be governed by the nature of the substituents of the ester group, which is *syn* with respect to the entering nucleophile. It is thus not



**Scheme 6.**

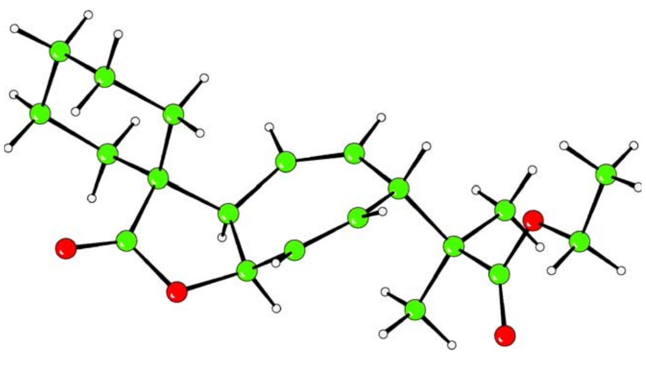


**Figure 1.** Molecular view of compound **9b** (oxygen atoms in red).

surprising to observe the formation of products due to an 'internal' rather than to a 'terminal' fixation of the second nucleophile.

In summary we have developed a new route for the synthesis of xanthanolide-related structures utilizing ketene acetals as nucleophiles. Application of this approach to the synthesis of more elaborate compounds than those presented herein is underway.

## Acknowledgements

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11. The same esters could be prepared by adding the corresponding lithium enolates to tropylium tetrafluoroborate.
12. Spectral data for **9b**: $R_f = 0.5$ (EtOAc/cyclohexane, 25:75). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.66; found, C, 72.06; H, 8.66; mp 110 °C; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ 5.9 (1H, dd, $J$ 12.2, 2.5), 5.67 (1H, dd, $J$ 13.7, 6.1), 5.64 (dd, 1H, $J$ 13.3, 5.1), 5.46 (ddd, 1H, $J$ 12.7, 5.1, 2.0), 5.18 (m, 1H), 4.10 (q, 2H, $J$ 7.1), 3.36 (t, 1H, $J$ 6.1), 3.02 (t, 1H, $J$ 6.1), 2.10 (m, 1H), 1.80–1.30 (m, 9H), 1.21 (t, 3H, $J$, 7.1), 1.13 (s, 3H), 1.21 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 180.10, 176.59, 130.99, 124.06, 76.66, 60.71, 49.61, 46.91, 45.44, 32.66, 30.38, 25.29, 22.75, 22.05, 21.64, 21.41, 14.19. Crystal data for **9b**: crystals of **9b** were grown from hexanes/dichloromethane. $C_{20}H_{28}O_4$: $M = 332.4$, triclinic, $a = 8.997(1)$, $b = 9.276(2)$, $c = 11.838(4)$ Å, $V = 902.8(4)$ Å$^3$, $T = 295$ K, space group $P$-1, $Z = 2$; Mo$K_\alpha$ ($\lambda = 0.71069$ Å), 3773 reflections collected, 3535 unique ($R_{\text{int}} = 0.03$), which were used in all least squares calculations, $R_1(F) = 0.0465$ (for 2370 reflections with $(F_o^2 > 3\sigma F_o)^2$, $R_2(F^2) = 0.0583$ (for all unique reflections). Crystallographic data for the structures of **6b** and **9b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary material, publication numbers CCDC 221173 and 221174. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].