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Facile Synthesis of Highly Functionalized Bicyclo[3.2.1]octanes as Potential Building Blocks for Various Natural Products

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Abstract: The cascade cycloaddition of 1-alkoxycyclohexadienolates **2** onto 2-chloro-2-cyclopropylideneacetate **4** yields 2-alkoxytricyclo[3.2.1.$0^{2,7}$]octane-2,6-diones **8** under acid catalysis. The tricyclooctanones **7** can be further elaborated, e. g. by Wittig olefination and reduction of the carbonyl group, or deprotonation at the bridgehead C-7 with subsequent alkylation, acylation or aldol reaction, before they are rearranged to the highly functionalized bicyclo[3.2.1]octane derivatives **10**, **11**, **13**, and **17**, respectively. The diones **8** can also be further manipulated, e. g. by regioselective Wittig olefination at C-2.

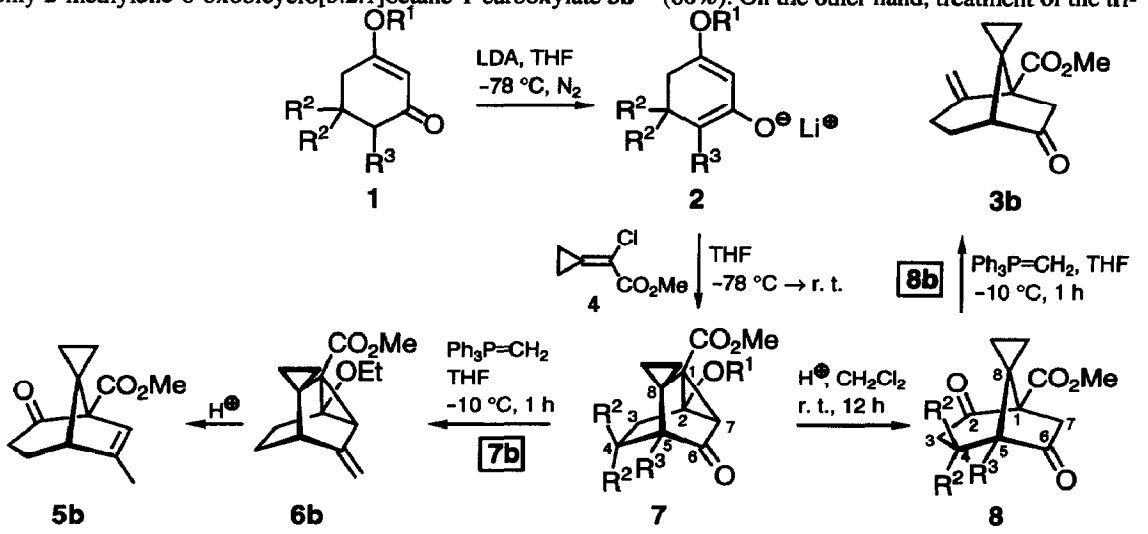
The bicyclo[3.2.1]octane ring system is a key structural entity of several tri- and tetracyclic sesqui- and diterpenes and their metabolites, such as cedrene,[1] cedrol,[1b] khusimone,[2] sativene,[3] gymnomitrol[4] and the gibberellins.[5] Moreover, bicyclo[3.2.1]octane derivatives have proved to be useful intermediates for the synthesis of important natural products such as 8-epiloganin[6] and taxol.[7] Although, the bicyclo[3.2.1]octane skeleton has most frequently been constructed by intramolecular alkylation,[3a,8] ring expansion[6a] or aldol reaction,[4a,c,8] Claisen condensation,[8] Pummerer based cyclization,[7b,8] reductive cyclization,[7a,8] and intramolecular cyclopropanation followed by selective cleavage of one of the newly formed bonds,[5,8] a number of approaches utilizing a Diels-Alder reaction have been reported[8] over the last few years. The facile formation of tricyclo[3.2.1.$0^{2,7}$]octane derivatives upon cascade cycloaddition[9] of methyl 2-chloro-2-cyclopropylideneacetate **4**, readily available in two short steps from ethylene and tetrachlorocyclopropene,[10] to cyclohexadienolates, prompted us to further elaborate on such compounds and their possible subsequent transformations to highly functionalized bicyclic skeletons. Especially the 1-alkoxy substituted derivatives were of interest, as they can undergo an acid catalyzed retro-aldol reaction to give bicyclo[3.2.1]octane derivatives, which are less easy to come by.

Indeed, a reasonably large number of lithium 1-alkoxycyclohexadienolates **2** generated from the corresponding 3-alkoxycyclohex-2-enones **1** with lithium diisopropylamide (LDA) react with the α-chloroacrylate **4** to give the tricyclic γ-ketoesters **7** in good yields (Table 1). Unfortunately, the configuration of the skeleton could not be controlled with a chiral auxiliary in the alkoxy group of **1**, as the diastereomeric ratio of the products **7h** from the (+)-menthyloxy derivative **1h** was 1.1 : 1. The allyl derivative **7i** (entry 9 in Table 1) was obtained by first alkylating the dienolate **2f** with allyl bromide, then generating the dienolate **2i** and adding it to the α-chloroacrylate **4**. This demonstrates an option for additional functionalization of the tricyclo[3.2.1.$0^{2,7}$]octanes **7**.

Treatment of these tricyclic γ-ketoesters **7** with an acid (e. g. aqueous HCl, CF_3COOH, *p*-TsOH) in dichloromethane affords the spirocyclopropanated 2,6-dioxobicyclo[3.2.1]octane-1-carboxylates **8** in excellent yields (see Table 1). Moreover, the two step process leading to these highly functionalized bicyclo[3.2.1]octane derivatives **8** (Scheme 1) was easily shortened into one step by working-up the reaction mixture

from **2** and **4** with an aqueous HCl instead of a saturated NH_4Cl solution (isolated overall yield of e. g. **8b** 96%).

For further elaboration on these skeletons **8** it is important that the two carbonyl groups can be differentiated, as was demonstrated for **8b** in its reaction with triphenylmethylenephosphorane (2.5 equiv.) yielding only 2-methylene-6-oxobicyclo[3.2.1]octane-1-carboxylate **3b**[11] (60%). On the other hand, treatment of the tricyclic γ-ketoester **7b** with $Ph_3P{=}CH_2$ (2.5 equiv.) afforded compound **6b** in 81% isolated yield, which was converted to the 6-methylbicyclo[3.2.1]oct-6-en-2-one **5b**[11] (94% yield). The tricyclic γ-ketoester **7c** with its two methyl substituents on C-4 did not react when treated with $Ph_3P{=}CH_2$ (2.5 equiv.) even for prolonged times at room temperature, probably due to steric hindrance of the phosphorane approaching the carbonyl group in **7c** from either side.



Scheme 1. (For details see Table 1).

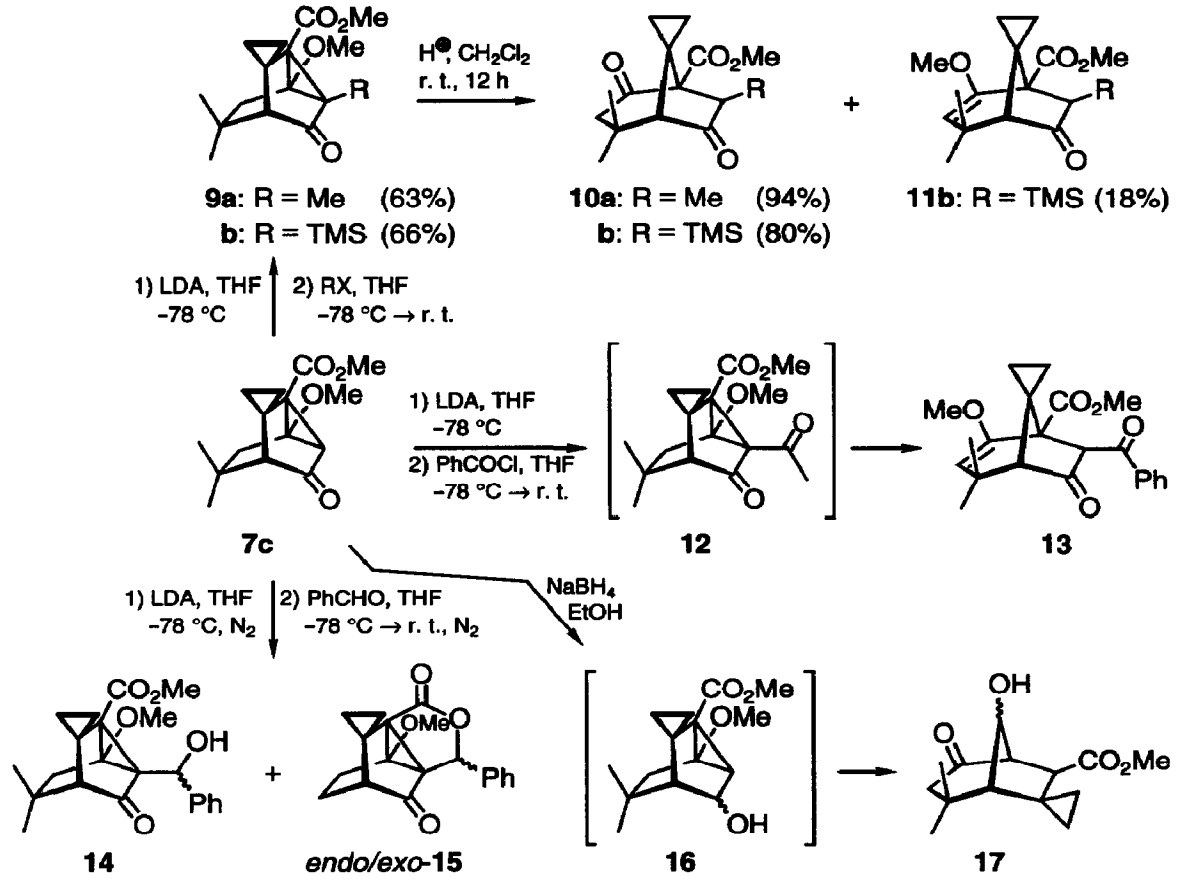
Table 1. 2-Alkoxy-6-oxotricyclo[3.2.1.$0^{2,7}$]octane-1-carboxylates **7** from Alkoxycyclohexadienolates **2** and Chlorocyclopropylideneacetate **4**, and their Transformation to 2,6-Dioxobicyclo[3.2.1]octane-1-carboxylates **8** (see Scheme 1)[11]

Entry	Starting Material	R^1	R^2	R^3	Product	Yield[a] (%)	Product	Yield (%)
1	**1a**	Me	H	H	**7a**	59	**8a**	98
2	**1b**	Et	H	H	**7b**	60	**8a**	98
3	**1c**	Me	Me	H	**7c**	86	**8b**	91
4	**1d**	Et	Me	H	**7d**	58	**8b**	93
5	**1e**	*i*-Pr	Me	H	**7e**	71	**8b**	95
6	**1f**	*n*-Bu	Me	H	**7f**	72	**8b**	94
7	**1g**	$CH_2CH{=}CH_2$	Me	H	**7g**	66	**8b**	93
8	**1h**	(+)-menthyl	Me	H	**7h**	67[b]	**8b**	–
9	**1i**	*n*-Bu	Me	$CH_2CH{=}CH_2$	**7i**	58	**8c**	99

[a] Isolated yield pure product after recrystallization (pentane) or flash chromatography on silica gel. – [b] Diastereomeric ratio 1.1:1.

Further functionalizations of compounds **7** and thereby also of compounds **8** could be achieved by deprotonation with LDA in THF e. g. of **7c** at C-7 and subsequent quenching with an electrophile. Thus methylation and silylation could be brought about with methyl iodide and chlorotrimethylsilane in 63 and 66%

yield respectively (Scheme 2).[11] It is quite remarkable that the tricyclic γ-ketoester **7c** is so easily deprotonated as it does not lead to a regularly stabilized enolate,[12] although the carbonyl group on C-6 exerts its usual electron withdrawing effect and thereby increases the kinetic acidity of the adjacent cyclopropylic proton. At



Scheme 2

least equally important, however, is the alkoxy group on the cyclopropane ring, as it can stabilize the lithiated species by chelation.[13] The substitution products **9a,b**, when treated with dilute aqueous HCl in dichloromethane at ambient temperature readily underwent ring-opening quantitatively. While **9a** gave only the bicyclic dione **10a**, the trimethylsilyl derivative **9b** yielded 18% of the methyl enol ether **11b** along with 80% **10b**. It is noteworthy that single diastereomers were formed in each case, most probably the *exo*-isomer, albeit the assignment has not been rigorously proved.[14] Treatment of **7c** with LDA followed by quenching with benzoyl chloride afforded the bicyclic 1,3-diketone **13** with a methyl enol ether moiety in 46% yield. Apparently, the C^2-C^7 cyclopropane bond in the triply acceptor substituted tricyclic product **12** breaks so easily that it opens up even at ambient temperature (Scheme 2). The anion generated from the tricyclic γ-ketoester **7c** with LDA could, however, be quenched with benzaldehyde to give the expected aldol product **14** (35% yield, diastereomeric ratio 4 : 1) along with the lactone **15** (15%, ratio 5 : 3). Recrystallization (CH_2Cl_2/ hexane) of the lactone **15** affords the pure *endo*-isomer, m. p. 126-128 °C, and from the mother liquor the *exo*-isomer of **15**, m. p. 144-145 °C (hexane), was isolated.[11,15]

Upon reduction with $NaBH_4$ in ethanol the tricyclic γ-ketoester **7c** gave the bicyclic alcohol **17** in 71% yield (ratio of diastereomers 95 : 5). This product must arise from a cleavage of the C^1-C^2 cyclopropyl bond[16] in the unstable tricyclic alcohol **16**.

This methodology appears to be widely applicable to the synthesis of highly substituted bicyclo[3.2.1]octane skeletons of many kinds. Especially the aldol reaction of compounds **7**, once optimized, can be extended to useful applications in the synthesis of natural products.

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11. All new compounds were fully characterized by their spectroscopic (IR, ^1H and ^{13}C NMR, MS) and satisfactory elemental analysis data.
12. For a similar carbonyl substituted bridgehead cyclopropyl anion see: (a) Wrobel, J.; Takahashi, K.; Honkan, V.; Lannoye, G.; Cook, J.M.; Bertz, S. H. *J. Org. Chem.* **1983**, *48*, 139. – (b) Nagaoka, H.; Kondo, Y.; Baba, A.; Yamada, Y. 108th Annual Meeting of the Pharmacentical Society of Japan, Abstract of Papers **1988**, p. 55.
13. For the importance of such a chelation see: (a) Padwa, A.; Wannamaker, M.W. *Tetrahedron Lett.* **1986**, *27*, 2555. – (b) Militzer, H.-C.; Schömenauer, S.; Otte, C.; Puls, C.; Hain, J.; Bräse, S.; de Meijere, A. *Synthesis* **1993**, 998. – In fact, the spirocyclopropanated methyl 2-methyl-6-oxotricyclo[3.2.1.$0^{2,7}$]octane-7-carboxylate,[9d] which has a methyl instead of a methoxy group at C-2, was only partially deprotonated with LDA in a control experiment carried out under the same conditions. When the anion solution was quenched with deuteromethanol, 42% deuterium incorporation was observed in the product; but quenching with methyl iodide did not yield any methylated product.
14. The COESY NMR spectrum was not conclusive, so the assignment will only be possible by X ray crystal structure analysis.
15. The methine proton of *endo*-**15** resonates at δ 5.45 and that of *exo*-**15** at δ 6.21 (J = 0.45 Hz). The resonances for the carbonyl carbon and the lactone carbon of *exo*-**15** appear at δ 199.9 and 168.3, whereas those of *exo*-**15** at δ 202.9 and 167.7, respectively, in the ^{13}C NMR spectrum.
16. For a similar case see : (a) Nagaoka, H.; Baba, A.; Yamada, Y. *Tetrahedron Lett.* **1993**, *34*, 1501. – (b) Nagaoka, H.; Shibuya, K.; Yamada, Y. *Tetrahedron Lett.* **1991**, *32*, 6741.

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