

One-pot Construction of the Oxapropellane Skeleton

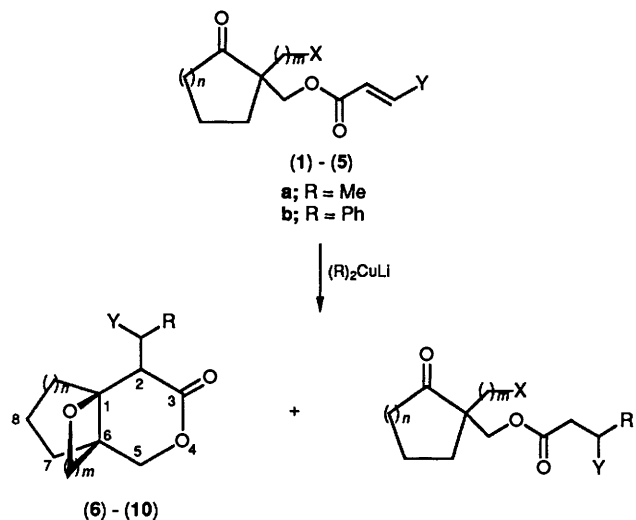
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1,4-Addition of diorganocuprates to the α,β -unsaturated esters (1)–(5) gave the oxapropellane skeleton, compounds (6)–(10), in a one-pot reaction, which proceeded *via* 1,4-addition, aldol condensation, and substitution.

Conjugate addition of diorganocuprates to Michael type acceptors such as enones is well known to be a valuable tool in chemical synthesis.¹ In particular, highly stereoselective 1,4-addition is useful for the solution of stereochemical problems encountered in the synthesis of natural products.² In addition, intermediate enolates generated by the conjugated addition of dialkylcuprates to α,β -enones (or esters) can undergo *O*- and/or *C*-trapping. For example, trapping with silyl halide affords silyl enol ethers, which are versatile synthetic intermediates, and reaction with an alkyl halide (or carbonyl function) forms the C–C bond (or aldol).³

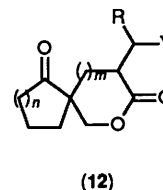
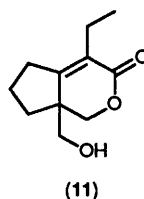
We describe a one-pot synthesis of the oxapropellane skeleton based on 1,4-addition followed by intramolecular aldol condensation, and subsequent substitution. As far as we know, this is the first case of a one-pot construction of this tricyclic skeleton by 1,4-addition. Substrate (3)⁴ was subjected to 1,4-addition using $(\text{Me})_2\text{CuLi}$, prepared from $\text{CuBr}\cdot\text{Me}_2\text{S}^5$ and MeLi^6 /ether at -30°C . The GM-MS spectrum [m/z 210 (M^+), 195, 123, and 55] of the oily product (8a) (50% yield) suggested that this product is a mixture of two diastereoisomers in the ratio of 7:1. In the ^{13}C NMR spectrum, the carbonyl function at δ 218.7 in substrate (3) disappeared, and a new quaternary carbon was observed at δ 94.4, in addition to the original quaternary carbon (δ 53.5). Disappearance of the vinyl protons in the 270 MHz ^1H NMR spectrum supported the 1,4-addition of the methyl function. The above spectroscopic data supported the proposed oxapropellane structure and excluded the possibility of the spiro lactone (12). Chemical evidence for the oxapropellane skeleton was obtained as follows. Compound (6a) obtained by similar 1,4-addition reaction of (1) was readily converted into the α,β -unsaturated lactone (11) by treatment with 2% KOH/MeOH for 10 min at room temperature. This finding indicates the presence of the oxetane ring at the β -position of the lactone carbonyl.

The stereochemistry of C-2 for each product was based on an analysis of the nuclear Overhauser effect difference spectrum (NOEDS) as exemplified in (6b). In (6b; 2 α -H), NOE between the 2-H and the 5-H was observed, but any NOE between the 2-H and the 11-H was not observed. This observation suggests that the lactone ring is in the boat form, and 2- CH_2Ph and 2-H occupy equatorial and axial(α)-positions, respectively. The observation of NOE between the 2- CH_2Ph and 5-H in (6b; 2 β -H) indicated that PhCH_2 function occupies the axial(α) configuration in the boat form.



Substrates	Oxapropellane Yields (%) (ratio of 2 α -H to 2 β -H)	Yields (%) of 1,4-addition products
(1; $m = n = 1$, $Y = \text{H}$, $X = \text{OTs}$)	(6a) 47 (6:1) (6b) 55 (7:1)	0 0
(2; $m = n = 1$, $Y = \text{Me}$, $X = \text{OTs}$)	(7a) 31 (2.5:1) (7b) 69 (*1)	21 0
(3; $m = 2$, $n = 1$, $Y = \text{H}$, $X = \text{Cl}$)	(8a) 50 (7:1) (8b) 32 (4:1)	0 6
(4; $m = 2$, $n = 1$, $Y = \text{Me}$, $X = \text{Cl}$)	(9a) 39 (1:1) (9b) 75 (*2)	30 8
(5; $m = 1$, $n = 2$, $Y = \text{H}$, $X = \text{OTs}$)	(10a) 61 (2:1) (10b) 49 (2:1)	0 2

* (1), (2): A mixture of four diastereoisomers (3:2:1:1).



Experimental

General Procedure.—Methyl lithium (1.04M in ether; 4.14 ml, 4.30 mmol) was added dropwise in a stirred suspension of CuBr·Me₂S (442 mg, 2.15 mmol) in ether (10 ml) at -30 °C under an Ar atmosphere. Next, substrate (3) (100 mg, 0.43 mmol) in ether (2 ml) was added dropwise at -30 °C, and the whole was stirred for 1 h, quenched by saturated aqueous NH₄Cl (30 ml), and extracted with ether. The ether extract was washed with 5% aqueous NaHCO₃, and brine, dried (Na₂SO₄) and evaporated under reduced pressure to leave an oily residue, which was purified by flash column chromatography on silica gel. The fraction eluted with 15% AcOEt in hexane (v/v) afforded (8a) (46 mg, 50%) as a mixture in the ratio of 7 (2 α -H) to 1 (2 β -H) as a colourless oil: * (8a) $\nu_{\max}(\text{film})$ 1 740, 1 450,

1 380, 1 100, and 1 060 cm⁻¹; $\delta_{\text{H}}(\text{CDCl}_3)$ 4.23, 4.26 (7:1) (1 H, d, J 11 Hz, 5-H), 4.10, 3.97 (7:1) (1 H, d, J 11 Hz, 5-H), 3.61–4.03 (2 H, m, 11-H₂), 2.47, 2.13 (7:1) (1 H, m, 2-H), and 1.07, 1.09 (7:1) (3 H, t, J 7.4 Hz, Me); $\delta_{\text{C}}(\text{CDCl}_3)$ 173.4 (s), 94.4, 95.0 (7:1) (s), 70.0, 71.6 (7:1) (t), 66.0, 66.2 (7:1) (t), 53.5 (s), 48.2, 50.0 (7:1) (d), 38.0, 38.7 (7:1) (t), 36.4 (t), 35.8 (t), 22.1 (t), 18.5 (t), and 13.3 (q); m/z (EI-MS) 210 (M^+ , 87%), 195(100), 123(90), 96(13), and 55(56).

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- 6 Commercially available MeLi (1M in ether, Kanto Chemicals, Japan) and PhLi (2M in cyclohexane-ether, Aldrich) were used.

* All compounds obtained in this manner are colourless oils, and gave satisfactory spectroscopic data. Selected spectroscopic data for representative products, (6a): $\nu_{\max}(\text{film})$ 1 745, 1 460, and 1 390 cm⁻¹; $\delta_{\text{H}}(\text{CDCl}_3)$ 4.56, 4.63 (6:1) (1 H, d, J 7 Hz, 11-H), 4.27, 4.31 (6:1) (1 H, d, J 7 Hz, 11-H), 4.33, 4.62 (6:1) (1 H, d, J 12 Hz, 5-H), and 4.13, 4.26 (6:1) (1 H, d, J 12 Hz, 5-H); $\delta_{\text{C}}(\text{CDCl}_3)$ 172.3 (s), 97.0, 95.7 (6:1) (s), and 47.4, 46.3 (6:1) (s); m/z (EI-MS) 196 (M^+ , 19%), 181(18), 166(24), and 81(100).

(10a): $\nu_{\max}(\text{film})$ 1 740, 1 460, and 1 385 cm⁻¹; $\delta_{\text{H}}(\text{CDCl}_3)$ 4.56, 4.53 (2:1) (1 H, d, J 7 Hz, 12-H), 4.46, 4.41 (2:1) (1 H, d, J 7 Hz, 12-H), and 4.16–4.40 (2 H, m, 5-H₂); $\delta_{\text{C}}(\text{CDCl}_3)$ 173.0 (s), 87.2, 86.0 (2:1) (s), and 36.0, 38.7 (2:1) (s); m/z (EI-MS) 210 (M^+ , 20%), 180(27), 141(15), 123(50), and 55(100)

(11): $\nu_{\max}(\text{film})$ 3 450, 1 710, and 1 690 cm⁻¹; $\delta_{\text{C}}(\text{CDCl}_3)$ 4.58 (1 H, d, J 11 Hz), 3.93 (1 H, d, J 11 Hz), 3.62 (1 H, d, J 11 Hz), and 3.42 (1 H, d, J 11 Hz); $\delta_{\text{C}}(\text{CDCl}_3)$ 165.5 (s), 161.9 (s), 126.2 (s), and 49.9 (s); m/z (EI-MS) 196 (M^+ , 40%), 178(14), 166(100), 149(32), and 121(69); $\lambda_{\max}(\text{EtOH})$ 241 nm (ϵ 6 480).

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