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A new and rapid access towards *exo*-methylene-δ-valerolactones from (cyclopropyl)methylstannanes

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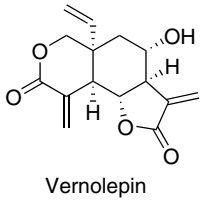
Abstract—Lewis-acid catalysed ring-opening of functionalised (cyclopropyl)methylstannane **10**, in the presence of aldehydes or ketones, was found to afford the corresponding aldol adducts in high yields. Subsequent lactonisation under acid catalysis led quantitatively to substituted *exo*-methylene-δ-valerolactones, some of them possessing a unique spirocyclic structure.

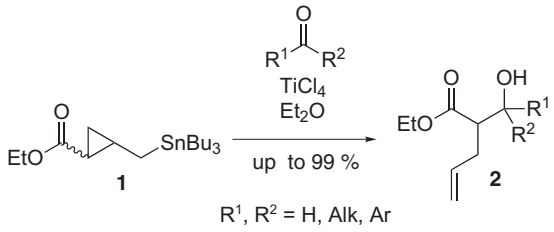
exo-Methylene lactones are ubiquitous fragments in a wide range of natural products possessing interesting biological properties. Consequently, a large amount of research has been devoted towards the efficient synthesis of such fragments, more specifically towards *exo*-methylene-γ-butyrolactones and *exo*-methylene-δ-valerolactones.[1] For example, both of these units are embedded in the skeleton of vernolepine, a sesquiterpene isolated from *Vernonia hymenolepis* and displaying antitumoral activities (Scheme 1).[2] In this letter, we wish to disclose our first results in the development of a new synthetic strategy leading to *exo*-methylene-δ-valerolactone subunits.

Recently, we have reported a new homoallylation methodology involving (cyclopropyl)methylstannanes such as **1** (Scheme 2).[3] In the presence of Lewis acids, such as $TiCl_4$, and carbonyl compounds, **1** undergoes regioselective ring-opening, followed by aldol condensation, to afford alcohols **2** in high yields.

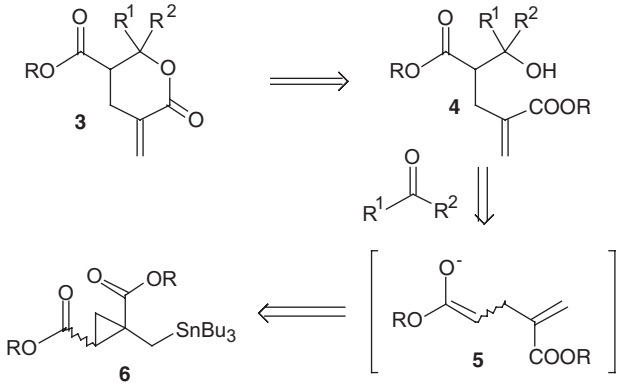


Vernolepin

Scheme 1.



Scheme 2.



Scheme 3.

Keywords: *exo*-Methylene lactone; Lactone; Spirobicycle; Cyclopropane; Homoallylation; Aldol reaction; Tin.
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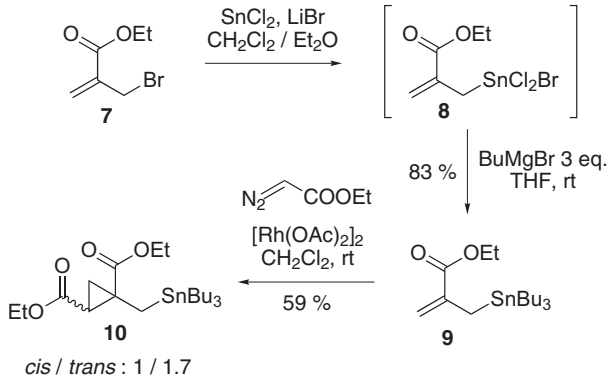
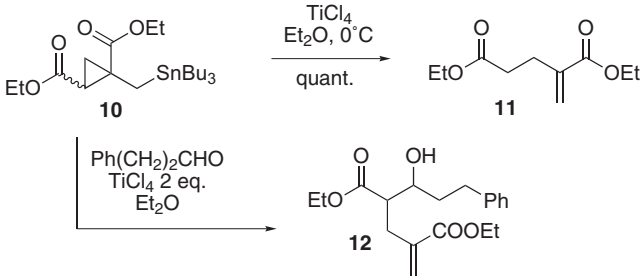


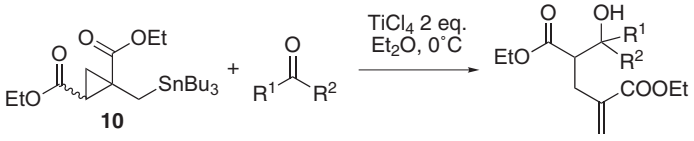
Scheme 4.

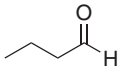
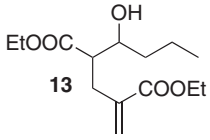
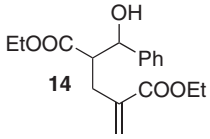
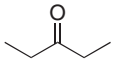
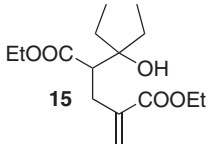
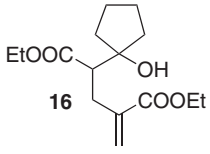
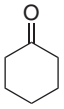
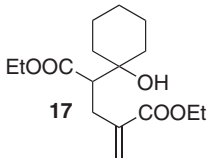
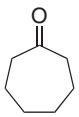
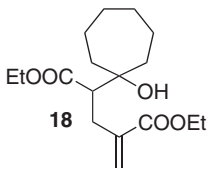


10	Temperature	Yield	12-*syn* / 12-*anti*
trans	0 °C	88 %	58 / 42
trans	-78 °C to rt	76 %	55 / 45
cis	0 °C	76 %	50 / 50

Scheme 5.

Table 1. One-pot ring-opening/aldol reaction



Entry	Electrophile	Product	Reaction time	Yield (%)[a]	*syn*/*anti*[b]
1		 13	2 h 30 min	91	71/29
2		 14	1 h	95	54/46
3		 15	2 h 30 min	90	—
4		 16	2 h	79	—
5		 17	1 h	80	—
6		 18	1 h 30 min	59	—

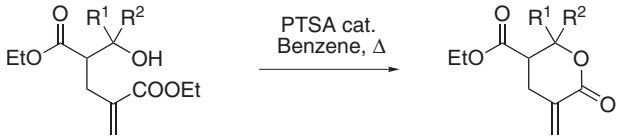
[a] All yields refer to pure, isolated product.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

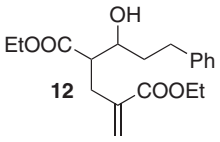
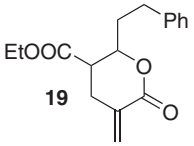
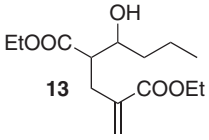
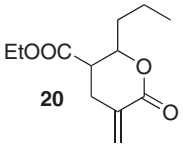
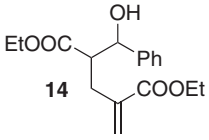
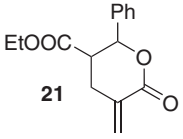
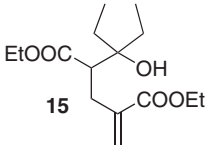
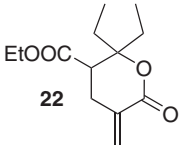
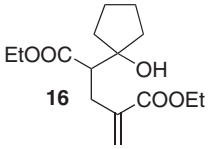
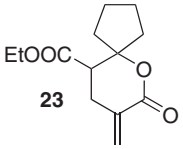
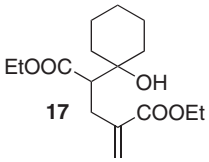
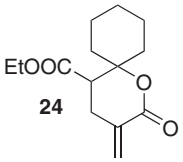
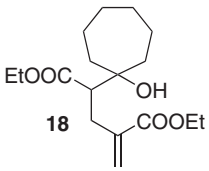
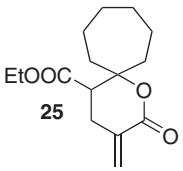
We envisaged that *exo*-methylene-δ-valerolactones such as **3** could be obtained by lactonisation of alcohols **4**. These products could in turn result from the one-pot ring-opening/aldol condensation of substituted (cyclopropyl)methylstannane **6** with various aldehydes or ketones, via the postulated enolate intermediate **5** (Scheme 3).

Accordingly, the synthesis of the key intermediate **10** was investigated. The readily available bromoester **7**[4] was efficiently transformed into the corresponding allyltin derivative **9** according to the protocol developed by Fouquet et al.[5] Subsequent rhodium-catalysed cyclopropanation of **8** with ethyl diazoacetate afforded (cyclopropyl)methylstannane **10** as a 1:1.7 mixture of *cis* and *trans* isomers, respectively (Scheme 4).

Having obtained the desired homoallylating reagent **10**, we next turned our attention to its Lewis-acid catalysed ring-opening. Gratifyingly, upon treatment with titanium tetrachloride, **10** underwent quantitative transformation into the corresponding bis-ester **11** (Scheme 5). This reaction was then carried out in the presence of dihydrocinnamaldehyde and afforded the expected aldol product **12** in good yields, though with modest diastereoselectivities.[6] The geometry of the cyclopropane or the

Table 2. Lactonisation of aldol products



Entry	Alcohol	Product	Reaction time (h)	Yield[a]
1	 **12**	 **19**	3	Quant.
2	 **13**	 **20**	3	Quant.
3	 **14**	 **21**	2	Quant.
4	 **15**	 **22**	6	Quant.
5	 **16**	 **23**	2	Quant.
6	 **17**	 **24**	4	Quant.
7	 **18**	 **25**	3	Quant.

[a] All yields refer to pure, isolated product.

reaction temperature was found to have negligible influence on the yield and the diastereoselectivity of the process.[7] Therefore, we decided to pursue our investigations with the mixture of *cis* and *trans* cyclopropanes **10**.

In order to determine the scope of this new transformation, the ring-opening/aldol reaction sequence was carried out in the presence of various aldehydes and ketones (Table 1). Aliphatic or aromatic aldehydes proved to be suitable substrates for this transformation (entries 1–2), as were dialkyl ketones (entry 3). Alcohols **13**–**15** were obtained in excellent yields. More interestingly, cyclic ketones were found to smoothly undergo aldol condensation, providing an entry towards 5-, 6- and 7-membered derivatives **16**–**18** (entries 4–6).

With various aldol products in hand, the lactonisation step was finally investigated. Initial attempts under basic conditions proved unsuccessful. In contrast, treatment of linear compounds **12**–**15** with catalytic amounts of PTSA in refluxing benzene led to the isolation of *exo*-methylene-δ-valerolactones **19**–**22** in quantitative yields after simple basic work-up (Table 2, entries 1–4). Much to our delight, the lactonisation of cyclic derivatives **16**–**18** proved to be equally efficient and gave access to unique spiro derivatives **23**–**25**, possessing a 5–6, 6–6 and 7–6 bicyclic structure, respectively (entries 5–7).[8]

In summary, we have developed an efficient method for the synthesis of functionalised *exo*-methylene-δ-valerolactones, involving a one-pot ring-opening/aldol condensation of a new (cyclopropyl)methylstannane derivative, followed by an acid-catalysed lactonisation.[9] An easy access to new spiro compounds of various ring-sizes has also been delineated. Current efforts are now focusing on the application of this methodology to the synthesis of natural products of biological interest.

Acknowledgements

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References and notes

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2. (a) Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 3596; (b) Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A. *J. Org. Chem.* **1969**, *34*, 3903.
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4. Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.
5. Fouquet, E.; Gabriel, A.; Maillard, B.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1995**, *132*, 590.
6. The diastereoisomeric relationship for aldol products was assigned on the basis of the frequency of resonance for the hydrogen vicinal to the hydroxyl group, which is consistently higher for the *syn* isomer than for the *anti* one.
7. The absence of influence of the cyclopropane geometry was already observed for aldol reactions with (cyclopropyl)methylstannane **1**. However, for this substrate, an important temperature effect on the diastereoselectivity was observed (see Ref. 3).
8. To the best of our knowledge, only one example of such *exo*-methylene spirolactone has been reported in the literature: Hon, Y.-S.; Liu, Y.-W.; Hsieh, C.-H. *Tetrahedron* **2004**, *60*, 4837.
9. *Typical experimental procedure*. Preparation of **16**: To a solution of (cyclopropyl)methylstannane **10** (100 mg, 0.204 mmol) and cyclopentanone (21 mg, 0.246 mmol) in dry diethyl ether (4 mL) at 0 °C was added $TiCl_4$ (410 μL, 0.410 mmol, 1 M solution in dichloromethane). The reaction mixture was stirred at 0 °C for 2 h, then was diluted with dichloromethane (20 mL) and quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column-chromatography (silica gel, petroleum ether–diethylether, 2:1) to give **16** as a colourless oil (46 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) 6.12 (1H, d, $J = 1.9$ Hz), 5.55 (1H, s), 4.20 (2H, q, $J = 7.6$ Hz), 4.10 (2H, q, $J = 6.7$ Hz), 3.00 (1H, broad s), 2.69–2.78 (3H, m), 1.51–1.96 (8H, m), 1.30 (3H, t, $J = 6.7$ Hz), 1.21 (3H, t, $J = 7.6$ Hz). ^{13}C NMR (63 MHz, $CDCl_3$) 175.79, 166.58, 138.25, 126.55, 82.10, 60.70, 60.42, 53.29, 40.18, 37.41, 31.78, 23.79, 14.17. IR (film) 3519, 2962, 2873, 1727, 1714, 1631, 1373, 1146, 1027. MS (APCI) *m/z*: 284.7 ($M+H^+$, 2), 220.9 (65), 192.9 (95), 165.0 (40), 147.0 (53), 119.0 (100). Preparation of **23**: To a solution of alcohol **16** (37 mg, 0.130 mmol) in benzene (6 mL) was added monohydrated PTSA (2 mg). The reaction mixture was refluxed for 2 h, then was diluted with dichloromethane (20 mL) and quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give **23** as a colourless oil (32 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) 6.48 (1H, s), 5.61 (1H, s), 4.16 (2H, q, $J = 7.6$ Hz), 2.83–2.98 (3H, m), 1.60–2.01 (8H, m), 1.25 (3H, t, $J = 7.6$ Hz). ^{13}C NMR (63 MHz, $CDCl_3$) 171.32, 164.86, 131.76, 128.65, 91.75, 61.14, 45.78, 38.71, 36.05, 28.47, 23.60, 23.54, 14.09. IR (film) 3434, 2964, 2876, 1731, 1627, 1306, 1182. MS (APCI) *m/z*: 238.9 ($M+H^+$, 100), 224.8 (35), 192.9 (45).