COMMUNICATION

Synthesis of δ-lactones from 2-alkynyl epoxides and 4-alkynyl-1,3-dioxolan-2-ones by palladium catalysed carbonylation and conjugate nucleophilic addition

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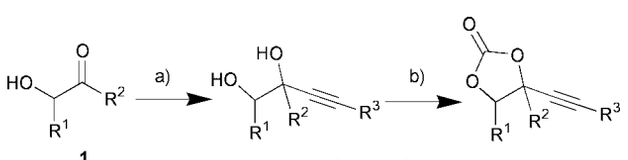
Palladium catalysed carbonylation of both 4-alkynyl-1,3-dioxolan-2-ones and alkynyl epoxides occurs under mild conditions to give methyl 5-hydroxy-2,3-dienoates which are converted to γ,δ-unsaturated δ-lactones by tandem conjugate addition–cyclisation with lithium dimethylcuprate or to methyl (*E*)-5-hydroxypent-3-enoates by stereoselective reduction with sodium borohydride.

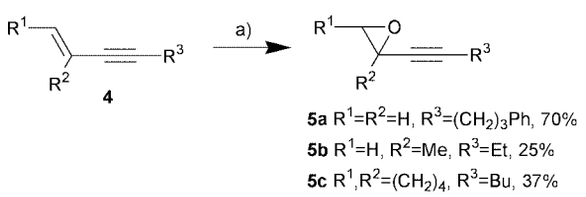
δ-Lactones are found in a wide variety of biologically important natural products[1] and have been isolated from organisms carrying genetically modified polyketide synthases.[2] We have recently reported[3] the synthesis of γ,δ-unsaturated δ-lactams by palladium catalysed carbonylation of 5-vinyloxazolidinones and were interested in extending our studies to the synthesis of the corresponding δ-lactones. This lactam formation, which is thought to involve the carbonylation of a π-allyl palladium intermediate, occurs at high pressures (70 atm CO). In contrast, the carbonylation of vinylpalladium intermediates occurs under much milder conditions,[4] and so we planned to use the alkynyl dioxolanones **3** rather than the corresponding vinyl species. Palladium catalysed carbonylation of 4-alkynyl-1,3-dioxolan-2-ones **3** and the corresponding epoxides **5** is known[5,6] to lead to alkyl 5-hydroxypenta-2,3-dienoates **6**. In this Communication we report the stereocontrolled conjugate addition of nucleophiles to the electron deficient 2,3-double bond of allenes **6** to give γ,δ-unsaturated δ-lactones in the case of lithium dimethylcuprate, and methyl (*E*)-5-hydroxypent-3-enoates in the case of sodium borohydride. Dioxolanones **3a–c** were prepared by the addition of 1-lithioalkynes to α-hydroxy ketones **1** to give the corresponding diols **2** followed by cyclisation[7] by treatment with methyl chloroformate (Scheme 1).



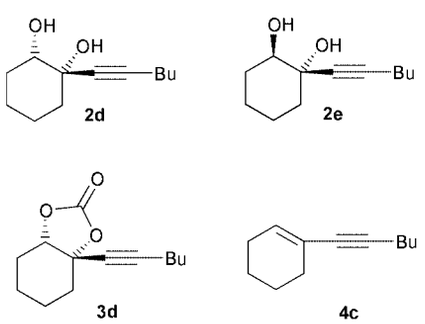
Scheme 1 *Reagents and conditions*: (a) $R^3C{\equiv}CLi$ (2.2 eq.), THF, 0 °C to rt, 2 h (**2c** was produced as a 2.5 : 1 mixture of diastereoisomers); (b) Et_3N (8 eq.), MeOCOCl (6 eq.), CH_2Cl_2, rt, 20 h.

Oxidation of enynes **4** with MCPBA[6] (Scheme 2) gave the corresponding alkynyl epoxides **5a–c** in very variable yields which were not improved by the use of buffered conditions. On one attempt, the oxidation of hex-1-ynylcyclohexene **4c** gave the diols **2d** (10%) and **2e** (8%) as the only identifiable products. The *syn*-diol **2d** was converted to the corresponding dioxolanone **3d** in 47% yield by treatment with methyl chloroformate.

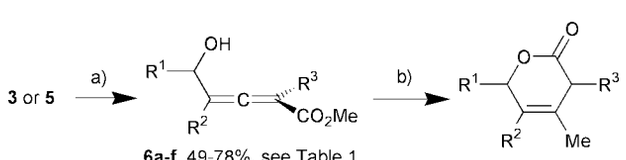
Tsuji and Mandai have reported[8] the carbonylation of alk-2-ynyl carbonates [$Pd(PPh_3)_4$ (2 mol%), CO (1–30 atm), MeOH].



Scheme 2 *Reagents and conditions*: (a) MCPBA (1.3 eq.), CH_2Cl_2, 0 °C to rt.



Dixneuf and co-workers[5] used harsher conditions [$Pd(dba)_2$ (2 mol%), PBu_3 (10 mol%), CO (50 atm)] for highly substituted alkynyldioxolanones and Piotti and Alper[6] reported the carbonylation of alkynyl epoxides [$Pd(Ph_2PMe)_4$ (1 mol%), CO (20 atm), MeOH, rt]. We found that the palladium catalysed carbonylation of alkynyldioxolanones **3a–d** and alkynyl epoxides **5a–c** proceeds in good yields under very mild conditions [$Pd(PPh_3)_4$ (1 mol%), CO (1 atm), MeOH, rt, 18 h] (Table 1, Scheme 3).



Scheme 3 *Reagents and conditions*: (a) $Pd(PPh_3)_4$ (1 mol%), CO (1 atm), MeOH, rt, 18 h; (b) Me_2CuLi (2.2 eq.), Et_2O, −78 to −40 °C.

The dioxolanone **3d** gave the allene **6d** in 70% yield whereas the corresponding epoxide **5c** gave the same allene in just 53% yield under our conditions (Table 1). As expected,[6] the carbonylation appeared to proceed with high diastereoselectivity. A 2.5 : 1 mixture of diasteroisomers of dioxolanone **3c** was transformed into a 2.5 : 1 mixture of diastereoisomers of allene **6c**. Similarly, the carbonylation of dioxolanone **3d** (a single diastereoisomer) and epoxide **5c** both gave the allene **6d** as a single diastereoisomer (by ^1H NMR).

Although nucleophilic addition to allene esters (most commonly to dimethyl penta-2,3-dienoate) has been reported[9] there are to our knowledge no reports concerning the addition of

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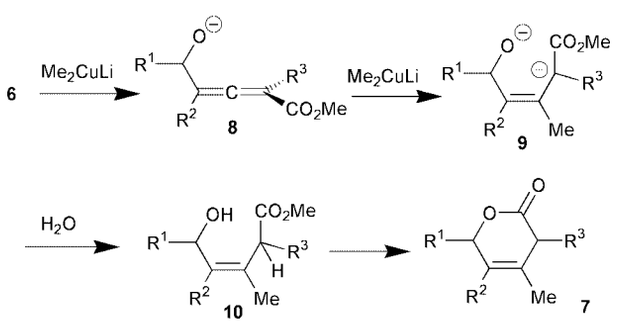
Table 1

SM [a]	R^1	R^2	R^3	Allene (% yield) [b]	Lactone (% yield) [b]
3a	H	Me	Bu	**6a** (76)	**7a** (60)
3b	H	Me	Ph	**6b** (49)	**7b** (56)
3c [c]	Me	Me	Ph	**6c** (51) [c]	**7c** (55) [e]
3d	$(CH_2)_4$		Bu	**6d** (70) [d]	**7d** (53) [e]
5a	H	H	$(CH_2)_3Ph$	**6e** (52)	**7e** (54)
5b	H	Me	Et	**6f** (78)	**7f** (53)
5c	$(CH_2)_4$		Bu	**6d** (53) [d]	

[a] Starting material. [b] Isolated yield. [c] A 2.5:1 mixture of diastereoisomers (^{1}H NMR). [d] A single diastereoisomer (^{1}H NMR). [e] A 1:1 mixture of diastereoisomers (^{1}H NMR).

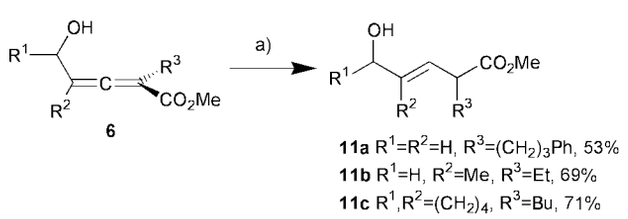
nucleophiles to alkyl 5-hydroxy-2,3-dienoates. We were pleased to find that addition of two molar equivalents of lithium dimethylcuprate to the allenes **6a**–**f** gave rise to the corresponding δ-lactones **7a**–**f** in 53–60% yields (Table 1, Scheme 3).[10] This process (Scheme 4) may involve[11] the stereoselective cuprate



Scheme 4

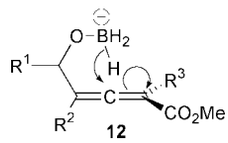
addition to the less hindered face of the 2,3-double bond of the alkoxide **8** (the size of the R^1CHO^- group may well be increased by metal ion coordination to the alkoxide) to give the (3*Z*)-enolate **9**. Protonation of this species occurs in the work-up since quenching the reaction of **6a** with D_2O gave the pyran-2-one **7a** deuterated at the 3-position. No hydroxy ester intermediate **10** is observed and, if formed, it must cyclise rapidly to the lactone **7**. The cuprate addition appears to be *Z*-stereoselective since we did not observe any of the *E*-hydroxy ester (corresponding to **10**), which would be unable to cyclise. Protonation of the enolate **9** is not stereoselective since lactones **7c** and **7d** are formed as 1:1 mixtures of diastereoisomers (Table 1).

In order to extend this scheme to the synthesis of naturally occurring sugar derivatives, we were interested in using a hydride nucleophile. Naruse *et al.* have reported[9b] the reduction of dimethyl penta-2,3-dienoate with $LiAlH_4$–$AlCl_3$. We chose to investigate the use of sodium borohydride as a more convenient alternative (Scheme 5). Reduction of allene **6e** [$NaBH_4$ (2.2



Scheme 5 *Reagents and conditions*: (a) $NaBH_4$ (2.2 eq.), EtOH, rt, 2 h.

eq.), EtOH, rt, 2 h][12] gave in 53% yield a mixture of the β,γ-unsaturated ester **11a** together with the corresponding α,β-unsaturated isomer in a ratio of 5:1. The *E*-alkene geometry of **11a** was assigned on the basis of the coupling constant (14.5 Hz) between the protons on the double bond. Allene **6f** was reduced to the corresponding β,γ-unsaturated ester **11b** in 69% yield. In this case none of the corresponding α,β-unsaturated ester was detected. The alkene is assumed to be *E* by analogy to the stereochemistry of **11a**. Reduction of allene **6d** gave the β,γ-unsaturated ester **11c** in 71% yield as a 1:1 mixture of diastereoisomers (these are assumed to be *E*-alkenes differing in the relative stereochemistry of C2 and C5 resulting from a non-stereoselective enolate protonation). The selective formation of *E*-alkenes can be explained on the basis of initial deprotonation of the OH group by borohydride, followed by internal delivery of hydride by the resulting alkoxyborohydride species **12**.



We are currently investigating the mechanisms of these reactions, the control of stereoselectivity, and the elaboration of the products to sugar-derived targets.

Acknowledgements

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10 *Typical procedure*; the synthesis of 4,5-dimethyl-3-phenyl-3,6-dihydropyran-2-one **7b**: MeLi (2.2 ml of 1.6 M solution in Et_2O, 3.6 mmol) was added to copper(I) iodide (344 mg, 1.8 mmol) in Et_2O (10 ml), under nitrogen at 0 °C. The suspension was stirred for 2 min, then cooled to −78 °C and a solution of methyl 5-hydroxy-4-methyl-2-phenylpenta-2,3-dienoate **6b** (197 mg, 0.9 mmol) in Et_2O (3 ml) was added. The reaction mixture was stirred for 45 min, and then a solution of NH_4Cl(aq)–MeOH–NH_3(aq) [15:10:4] (15 ml) was added to quench the reaction. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 ml). The combined organic layers were washed with H_2O (30 ml), brine (2 × 30 ml), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude material by column chromatography (EtOAc–petrol, 1:6) afforded the δ-lactone **7b** (100 mg, 56%) as a yellow oil. ν_{max}/cm^{-1} (film) 2916, 1741, 1650, 1597, 1495; δ_H (500 MHz, $CDCl_3$) 1.66 (3H, s, one of $CH_3C{=}CCH_3$), 1.80 (3H, s, one of $CH_3C{=}CCH_3$), 4.12 (1H, s, PhC*H*O), 4.63 (1H, d, *J* 16, one of CH_2O), 4.88 (1H, d with fine splitting, *J* 16, one of CH_2O), 7.26–7.35 (5H, m, Ar-H); δ_C (125MHz, $CDCl_3$) 14.26, 16.77, 51.48, 71.99, 123.65, 125.56, 127.80, 127.94, 128.99, 136.11, 170.53; *m/z* 202 (M^+, 27.5%), 158 (62), 143 (100), 128 (41), 91 (11), 77 (7); Found: (M^+) 202.0990. $C_{13}H_{14}O_2$ requires 202.0994.

11 For a discussion of the mechanism of cuprate addition to an allenic ketone see: J. Berlan, J.-P. Battioni and K. Koosha, *Tetrahedron Lett.*, 1976, 3355.

12 *Typical procedure*; the synthesis of methyl (*E*)-2-ethyl-5-hydroxy-4-methylpent-3-enoate **11b**: $NaBH_4$ (53.3 mg, 1.41 mmol) was added

to methyl 2-ethyl-5-hydroxy-4-methylpenta-2,3-dienoate **6f** (100 mg, 0.588 mmol) in dry ethanol (5 ml) under nitrogen at room temperature. The reaction mixture was stirred for 2 h, quenched with NH_4Cl (5 ml), and the product extracted into EtOAc (10 ml). The organic layer was removed and washed with NH_4Cl (5 ml), sat. $NaHCO_3$ (5 ml), brine (5 ml), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude material by column chromatography (EtOAc–petrol, 1 : 10 to 1 : 1) gave the ester **11b** as a clear oil (70 mg, 69%). δ_H (500 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.5, CH_3CH_2), 1.43–1.75 (2H, m, CH_3CH_2CH), 1.63 (3H, d, *J* 1.5, $CH_3C{=}CH$), 1.97 (1H, br s, OH), 3.13 (1H, dt, *J* 7.0, 9.5, $CH_3CH_2CH{=}C$), 3.6 (3H, s, CH_3OCO), 3.95 (2H, s, CH_2OH), 5.35 (1H, qd, *J* 1.5, 9.5, HC=C); δ_C (125 MHz, $CDCl_3$) 11.6, 13.9, 26.0, 45.8, 51.7, 68.1, 123.0, 137.9, 175.0; ν_{max}/cm^{-1} (film) 3421 (br), 2964, 2875, 1736; *m*/*z* 172 (M^+, 0.3%) 155 (3), 140 (100); Found (M^+) 172.10964. $C_9H_{16}O_3$ requires 172.10994.