Total synthesis of (±)-cinnamolide and (±)-methylenolactocin–an approach to butenolides using *S*-alkoxycarbonyl xanthates

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The total synthesis of (±)-cinnamolide 9 and (±)-methylenolactocin 15 is accomplished using as the key step a radical cyclisation involving alkoxycarbonyl radicals derived from *S*-alkoxycarbonyl xanthates.

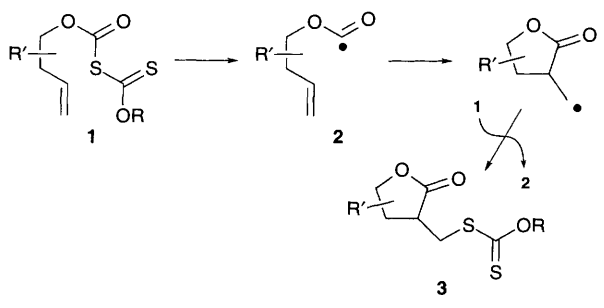
In the rapidly growing field of synthetic free radical chemistry, there is a continuous interest in new methods of radical generation.[1] The major drawback of metal hydride based methods is their essentially reductive character, and consecutive loss of functionality following carbon–carbon bond formation. In the special case of alkoxycarbonyl radicals,[2] if the cyclisation can be followed by transfer of a potential leaving group, then a simple β-elimination step would provide an easy access to butenolides—a structural subunit of many important naturally occurring substances. Here we describe the application of *S*-alkoxycarbonyl dithiocarbonates (xanthates)[3,4] in the total synthesis of (±)-cinnamolide **9** and (±)-methylenolactocin **15**, representing two common structural patterns found in naturally occuring butenolides.[5]

The key transformation, outlined in Scheme 1, offers several advantages over previously described methods[2] for the generation and capture of alkoxycarbonyl radicals: (*a*) group transfer cyclization delivers cyclized products (*i.e.* xanthate derivatives **3**) suitable for further functional transformations; (*b*) the radical precursor is the transfer agent as well, and therefore there is no need for an external chain-carrying reagent; and (*c*) there is no premature trapping of the uncyclized radical **2** since its reaction with **1** is degenerate, allowing reactions to be performed under relatively high concentrations of reactants.[3,4]

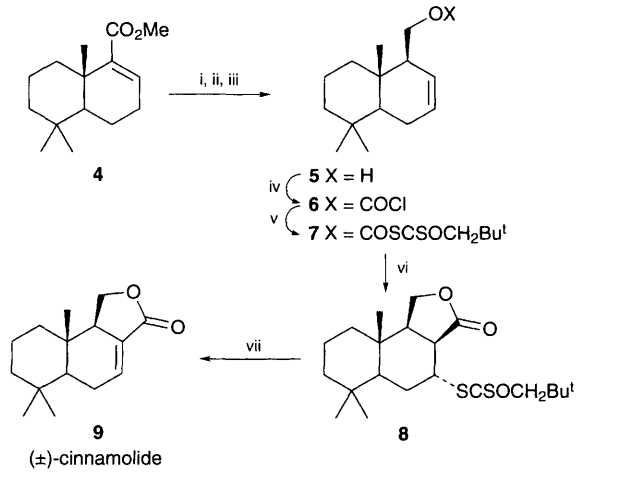
The synthesis of (±)-cinnamolide **9**,[6] a member of the drimane class of terpenoids,[7] is shown in Scheme 2. Isomerisation of the known ester **4**[8] followed by $LiAlH_4$ reduction afforded the unsaturated alcohol **5**, which was converted into the corresponding xanthate derivative **7** *via* chloroformate **6**. Upon irradiation with visible light (500 W, tungsten filament lamp, toluene, reflux), a smooth rearrangement took place affording the xanthate derivative **8** as a single diastereoisomer in 51% isolated yield. Treatment of **8** with DBU gave (±)-cinnamolide **9** as a colourless crystalline compound (80%, mp 83–85 °C, lit., 85–85.5 °C,[6c] spectral properties identical with those previously reported).

Methylenolactocin **15**, isolated from the culture filtrate of *Penicillium* sp.,[9] belongs to the large group of α-methylene-γ-butyrolactone antibiotics. Its antitumor and selective antibacterial activity, along with its relatively high level of functionalization and proclivity towards isomerisation make this small molecule an interesting synthetic target. Several total and formal syntheses of methylenolactocin have been reported.[10]

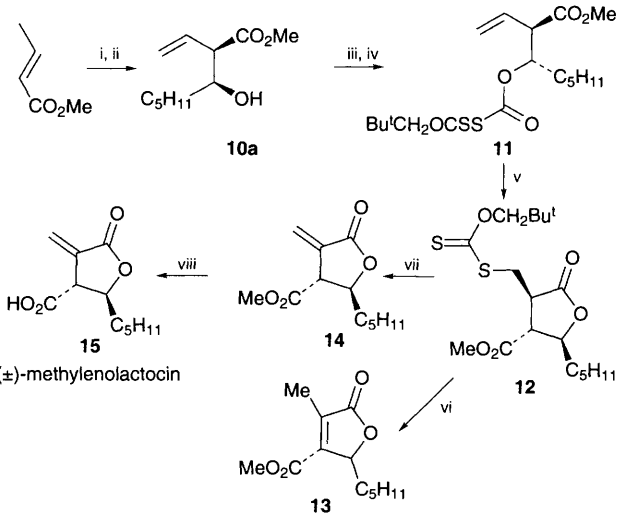
Our approach is displayed in Scheme 3. Addition of methyl crotonate anion to hexanal gave a quantitative yield of **10** as 1 : 1



Scheme 1



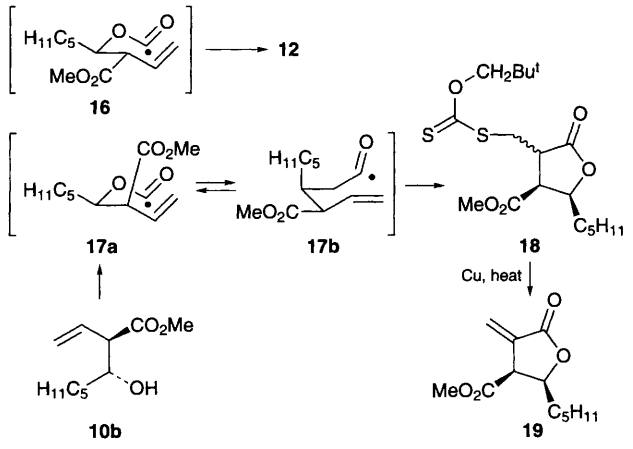
Scheme 2 *Reagents and conditions*: i, LDA, HMPA, THF, −78 °C; ii, HCl aq., 65%; iii, $LiAlH_4$, THF, 97%; iv, $COCl_2$, THF, PhMe, room temp., 0.5 h; v, $NaSC(S)OCH_2Bu^t$ acetone, room temp., 0.5 h; vi, hv (500 W tungsten lamp), PhMe, 111 °C, 9.5 h, 51% from **5**; vii, DBU, $CHCl_3$, room temp., 15 min., 80%



Scheme 3 *Reagents and conditions*: i, (*a*) LDA, THF, HMPA, −78 °C; (*b*) $C_5H_{11}CHO$, 100%; ii, separation of isomers, SiO_2; iii, $COCl_2$ THF, PhMe, room temp., 20 h; iv, $NaSC(S)OCH_2OBu^t$, acetone, room temp., 1 h; v, hv (500 W tungsten lamp), PhMe, 110 °C, 5.5 h; 63% from **10**; vi, DBU (or DBN, Et_3N, $KHCO_3$/18-K-6, *etc*;) 80%; vii, copper powder, 180 °C, 1 mmHg, 63%; viii, 6 mol dm^{-3} HCl butanone, reflux, 2 h, 75%

diastereoisomeric mixture. After separation of isomers, treatment of **10a** with phosgene followed by sodium neopentylxanthate afforded the radical precursor **11** which upon irradiation with visible light yielded the crystalline cyclic xanthate derivative **12** as a single diastereoisomer (63% from **10**, mp 79–81 °C). It is interesting in this respect to note that when isomer **10b** was submitted to the same sequence of reactions (iii, iv, v), a 2 : 1 mixture of diastereoisomers **18** was obtained. The relative stereochemistry of intermediates **10a**, **10b**, **12** and **18** was deduced from methylenolactocin methyl ester **14** and *epi*-methylenolactocin methyl ester **19**, whose configuration was established by NOE experiment. The stereochemical outcome of cyclizations can be explained assuming a chair-like transition state with strong preference of all substituents for pseudoequatorial positions. In this way, a single all-*trans* isomer **12** is obtained from **16**, whereas conformational equilibrium between **17a** and **17b** gives rise to the mixture of diastereoisomers **18** (Scheme 4).

Unfortunately, all our attempts to accomplish the xanthate elimination from lactone **12** under basic conditions as in the case of cinnamolide were unsuccessful. We invariably obtained regioisomer **13** as the only product. However, pyrolytic elimination of **12** in presence of copper powder and distillation of the product as formed afforded methylenolactocine methyl ester **14** in 62% isolated yield. Acidic hydrolysis of **14** under the previously described conditions[10e] furnished crystalline (±)-methylenolactocin **15** (mp 54–56 °C, recryst. from ethyl acetate–hexane, lit.,[10f]: oil), with ^{1}H and ^{13}C NMR spectra identical to published data.



Scheme 4

This is perhaps the shortest synthesis of methylenolactocin; it also demonstrates the applicability of the xanthate based radical process for the construction of delicate lactone containing structures. In principle, the starting homoallylic alcohol **10a** can be made in optically pure form by applying the now well established asymmetric aldol technology.[11]

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