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A new approach to the synthesis of polycyclic structures

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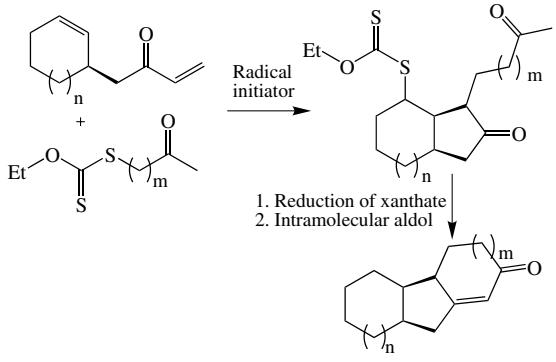
This paper is dedicated with respect and affection to the memory of Anne Ghosez-Giese

Abstract—A general, convergent approach to the synthesis of polycyclic structures has been developed, based on the tandem radical addition/cyclisation of xanthates to dienones followed by an ionic ring closure to give, finally, a number of variously substituted tricyclic compounds.

Radical cyclisations are among the most powerful and versatile reactions available for the construction of mono- and polycyclic systems.[1] However, many radical processes can only easily be applied to intramolecular radical cascades. The radical chemistry of xanthates offers a flexible method for the creation of carbon–carbon bonds in either an intramolecular or, more importantly, an intermolecular fashion.[2] By combining both classes of bond forming reactions in a radical sequence, it is possible to assemble quickly complex carbon frameworks. In addition, variation of the functionality present on the starting xanthate allows further ionic cyclisations.

The general concept is outlined in Scheme 1. Addition of a xanthate containing a suitably located ketone group to the diene should result in the formation of the *cis*-fused bicyclic compound as indicated in the first step. The xanthate group could then be reductively cleaved or used to introduce various functional groups and an intramolecular aldol-crotonisation reaction would finally lead to a tricyclic structure.

Dienes **4** and **8**, derived, respectively, from (±)-isophorol and 3-methylcyclopent-2-enone were chosen as model substrates. Treatment of (±)-isophorol **1** with butyl vinyl ether in the presence of mercuric acetate afforded the corresponding allyl vinyl ether, which was not purified



Scheme 1. General route to polycyclic compounds.

but heated at 195 °C for 50 min in a sealed tube to afford the rearranged aldehyde **2**.[3] Exposure of the crude aldehyde to the action of vinyl magnesium bromide furnished the allylic alcohol, **3**, which was oxidised with IBX to enone **4** in an acceptable overall yield (Scheme 2).

Similarly, 3-methylcyclopent-2-enone, **5**, was converted to diene **8** by the same reaction sequence (Scheme 3), although in this case PCC was found to be a superior oxidising agent to IBX. As the Claisen rearrangement is stereospecific,[4] the use of an enantiopure alcohol would give access to chiral alkenes and hence allow absolute stereocontrol in the formation of the final polycyclic products.

Dienes **4** and **8** successfully underwent radical addition/cyclisation with α-xanthyl ketones, **9a**–**c**, to afford

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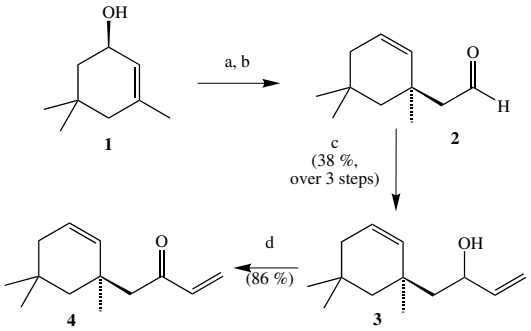
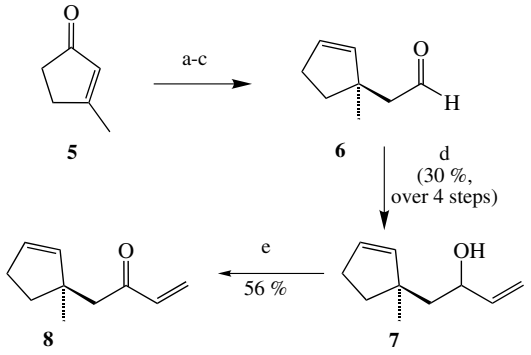
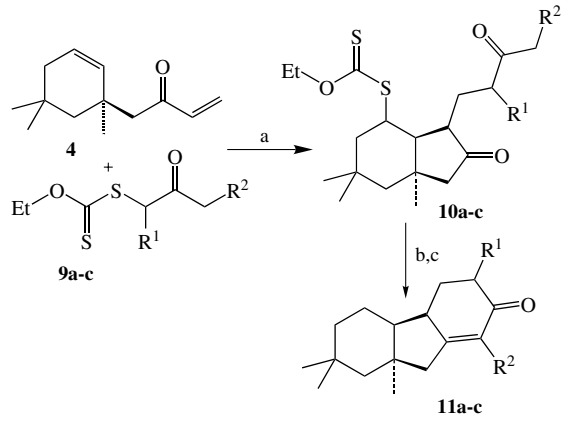


Scheme 2. Reagents and conditions: (a) butyl vinyl ether, $Hg(OAc)_2$, Δ, 24 h; (b) sealed tube, 195 °C, 50 min; (c) vinyl magnesium bromide, THF, 0 °C, 45 min; (d) IBX, DMSO, THF, 20 °C, 2 h.

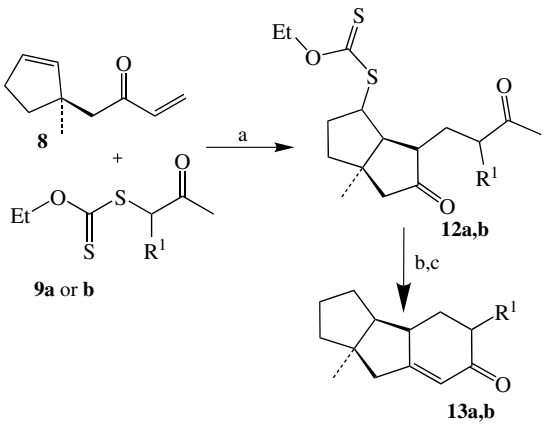


Scheme 3. Reagents and conditions: (a) DIBAL-H, THF, 0 °C 1 h; (b) butyl vinyl ether, $Hg(OAc)_2$, Δ, 18 h; (c) sealed tube, 190 °C, 30 min; (d) vinyl magnesium bromide, THF, 0 °C, 45 min; (e) PCC, DCM, 20 °C, 3 h.

cis-fused bicyclic compounds, **10a**–**c** and **12a**,**b**, respectively (Schemes 4 and 5). The bicycles were obtained as mixtures of diastereoisomers due to the chiral centre(s) α to the carbonyl(s). For convenience, the xanthate group, presumably in an *exo*-position, was reductively cleaved prior to the aldol condensation as it is known to be



Scheme 4. Reagents and conditions: (a) lauroyl peroxide (DLP) 5 mol% initially and then 3 mol% every 2 h, 1,2-dichloroethane, Δ, 12–24 h; (b) *n*-Bu_3SnH, AIBN, PhMe, Δ, 2 h; (c) KOH, ethanol, Δ, 30 min or 2 M $KOH_{(aq)}$, THF, Δ, 18 h.



Scheme 5. Reagents and conditions: (a) DLP 5 mol% initially and then 3 mol% every 2 h, 1,2-dichloroethane, Δ, 3-6 h; (b) *n*-Bu_3SnH, AIBN, PhMe, Δ, 2 h; (c) 2 M $KOH_{(aq)}$, THF, Δ, 18 h.

unstable under basic conditions; however, the presence of the xanthate is a powerful asset, since it could alternatively be used as a point of entry into the extremely rich ionic chemistry of sulfur or for the implementation of another radical sequence. Aldol condensation under basic conditions afforded the desired enones, **11a**–**c** and **13a**,**b**, in moderate yields. The reaction proved more problematic than initially anticipated and resisted attempts to find a general high yielding procedure. Table 1 gives the yields obtained for the three steps and the diastereoisomeric ratios (dr) of the enone products. As the stereocentres formed in the radical cascade are epimerisable (except the two at the *cis*-ring fusion) and as the reaction is carried out under thermodynamic control, the dr was expected to reflect the relative stabilities of the diastereomeric enone products. Such an effect was demonstrated by separating **10a** into two nonidentical mixtures of diastereoisomers. The two mixtures were then separately subjected to the reduction and aldol condensation procedures described above. After reduction of the xanthate moiety, ^1H and ^{13}C NMR analysis showed the major diastereoisomers to be different. However, after the aldol condensation the spectroscopic data of the tricyclic derivative **11a** obtained in both cases were identical.

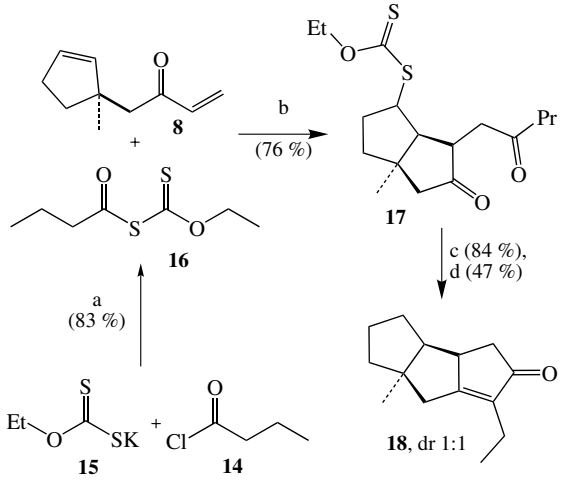
Acyl xanthates have been used for the formation of the corresponding alkyl xanthates via radical decarbonylation.[5] They have also been shown to undergo intramolecular radical additions to double bonds in moderate yields. However, there are only a few examples of intermolecular additions of acyl xanthates to double bonds. In our case, starting the cascade with an acyl radical would result in the formation of a cyclopentenone ring after the aldol condensation. To this end, acyl xanthate **16** was prepared from the corresponding acid chloride **14** and the potassium salt of xanthic acid (Scheme 6). The salt must be added portionwise over 1 h while the reaction temperature is maintained below −30 °C in order to avoid decomposition of the acyl xanthate by unreacted xanthate salt.[2]

The radical cascade was carried out by irradiating a refluxing solution of the diene and the xanthate with visible light. Reduction of the xanthate followed by

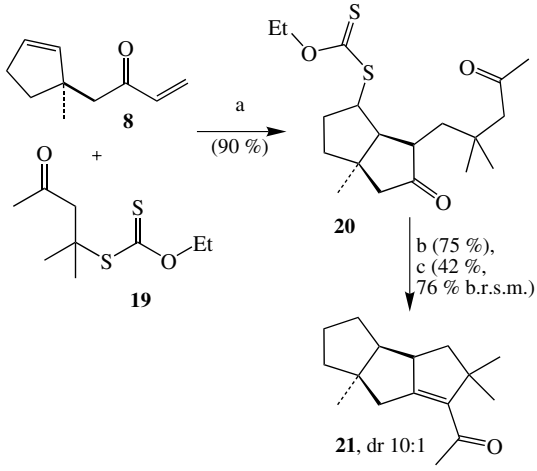
Table 1

Diene	Xanthate	R^1	R^2	Yield (%), radical cascade	Yield (%), reduction	Yield (%), aldol	dr (calcd by ^1H and ^{13}C NMR analysis of isolated products)
4	**9a**	H	H	**10a**, 73	76	**11a**, 61	4:1[a]
4	**9b**	Me	H	**10b**, 51	59	**11b**, 60	10:1[b]
4	**9c**	H	Me	**10c**, 75	60	**11c**, 54	10:1[b]
8	**9a**	H	H	**12a**, 75	76	**13a**, 46	10:1
8	**9b**	Me	H	**12b**, 65	91	**13b**, 65	1:1

[a] dr > 10:1 after crystallisation.
[b] Single diastereoisomer after crystallisation.



Scheme 6. Reagents and conditions: (a) acetone, −40 to −30 °C, 1 h; (b) visible light, PhMe, Δ, 3 h; (c) *n*-Bu_3SnH, AIBN, PhMe, Δ, 2 h; (d) 1 M NaOEt/ethanol, THF, Δ, 18 h.

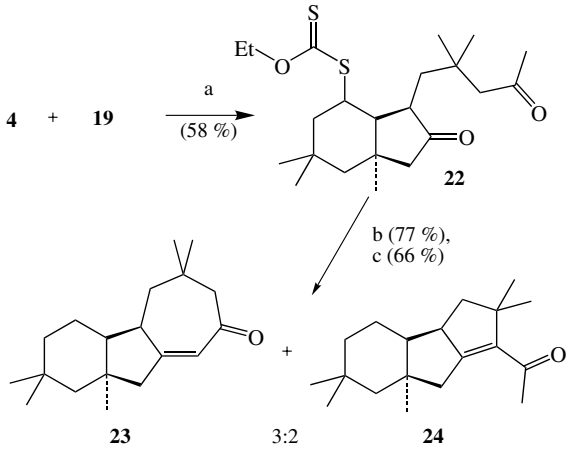


Scheme 7. Reagents and conditions: (a) DLP 5 mol% initially and then 3 mol% every 2 h, 1,2-dichloroethane, Δ, 6 h; (b) *n*-Bu_3SnH, AIBN, PhMe, Δ, 2 h; (c) *p*-TSA, THF, H_2O, Δ, 18 h.

aldol condensation gave enone **18** as a 1:1 mixture of diastereoisomers. Such [5.5.5]-fused ring systems are found in a number of natural products, including the triquinane family of terpenes.[6] This approach provides rapid access to the carbon framework of these compounds.

Another approach to linear triquinanes is to use xanthate **19**, a compound easily accessible by Michael addition of the xanthate salt to mesityl oxide under mildly acidic conditions.[7] In this case, the radical cascade would provide access to a tricyclic enone **21** containing the geminal dimethyl motif often found in polyquinane terpenes (Scheme 7). Indeed, the tertiary xanthate **19** readily underwent the radical cascade in excellent yield to afford the bicyclic compound **20**. Removal of the xanthate was followed by an acid catalysed aldol reaction. The thermodynamic enol formed under the acidic conditions gave rise to the [5.5.5]-fused ring system as the only product. The low yield was due to incomplete reaction of the starting material, which could be readily recovered by chromatography. The ease of creation of the quaternary centre in the intermolecular addition step is noteworthy.

Diene **4** also underwent the radical cascade with xanthate **19** to furnish bicyclic compound **22** (Scheme 8). Reduction of the xanthate was followed by Robinson annelation under basic conditions resulting in the formation of tricyclic derivatives **23** and **24**. Thus, by simply changing the conditions of the aldol condensation, it is possible to access a cyclopentenone or a cycloheptenone structure.



Scheme 8. Reagents and conditions: (a) DLP 5 mol% initially and then 3 mol% every 2 h, 1,2-dichloroethane, Δ, 6 h; (b) *n*-Bu_3SnH, AIBN, PhMe, Δ, 2 h; (c) KOH, ethanol, Δ, 18 h.

In summary, these preliminary model studies demonstrate the feasibility and flexibility of this strategy for the synthesis of polycyclic structures.[8] Various combinations of rings can be constructed by modifying both the xanthate and the dienone, as well as the conditions for the ionic cyclisation step. Last but not least, the stereochemistry follows ultimately from that of the initial allylic alcohol since the stereochemical information is conserved in the powerful Claisen rearrangement. This approach to polycyclic compounds is currently being applied to natural product synthesis.

Acknowledgements

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8. Typical experimental procedures: Lauroyl peroxide (DLP; 36 mg, 5 mol%) was added to a refluxing degassed solution of diene **4** (0.35 g, 1.82 mmol) and xanthate **9a** (1.79 g, 10.1 mmol, 5.5 equiv) in 1,2-dichloroethane (19 mL). Additional DLP (22 mg, 3 mol%) was added every 2 h to the refluxing solution until no starting material was observed by TLC. After cooling to rt, the solvent was removed in vacuo to give a crude oil, which was purified using column chromatography (diethyl ether–petroleum ether 1:9–2:8) to afford the bicycle **10a** (0.49 g, 73%) as a colourless oil.
A solution of the xanthate **10a** (0.49 g, 1.32 mmol) in toluene (13.2 mL) was heated at reflux for 30 min under a nitrogen atmosphere. Tributyltin hydride (0.52 mL, 1.96 mmol) was added and heating was continued for a further 1.5 h. AIBN (24 mg) was added and the reaction was heated at reflux for a further 2 h before cooling to rt. The solvent was removed in vacuo, the residue was redissolved in MeCN and washed with pentane. The MeCN was removed in vacuo and the crude oil purified by column chromatography (diethyl ether–petroleum ether 2:8) to afford the reduced product (0.25 g, 76%) as a colourless oil.
A solution of the dione (0.25 g, 1.0 mmol) in THF (10 mL) and 2 M $KOH_{(aq)}$ (2.0 mL) was heated at reflux for 18 h. After cooling to rt, 1 M $HCl_{(aq)}$ (10 mL) was added and the mixture was stirred for a further 5 min before the solution was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The crude residue was purified by column chromatography (diethyl ether–petroleum ether 2:8) to afford the enone **11a** (0.141 g, 61%, dr 4:1) as a colourless solid. Recrystallisation from petroleum ether afforded colourless needles (dr 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm): 5.85 (1H, d, $J = 2$ Hz, olefinic H), 2.78–2.74 (1H, m, CH), 2.50–2.45 (2H, m), 2.34–2.32 (2H, m), 2.18–2.13 (1H, m), 1.86–1.77 (1H, tt, $J = 14.4$ and 4 Hz), 1.59–1.48 (2H, m), 1.42–1.3 (2H, m), 1.26–1.20 (3H, m), 1.20 (3H, s, CH_3), 1.01 (3H, s, CH_3), 0.90 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 199.6 (CO), 174.5 (C olefinic), 122.6 (CH olefinic), 49.6 (CH_2), 49.1 (CH), 47.4 (CH_2), 42.6 (CH), 39.1 (C), 37.1 (CH_2), 34.6 (CH_3), 32.1 (CH_2), 30.4 (C), 28.1 (CH_2), 27.7 (CH_3), 26.7 (CH_3), 18.7 (CH_2). IR (CH_2Cl_2) ν_{max} (cm^{-1}): 2917s, 1734w, 1716w, 1667s. Combustion analysis: Found C 82.4%, H 10.3%; Required C 82.7%, H 10.4%. MS (CI) m/z (%): 233 (100%, MH).