Facile Ramberg–Bäcklund Reactions for the Synthesis of 2,3-Disubstituted Cyclopentenones; a Short Synthetic Route to Tetrahydrodicranenone B

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The Ramberg–Bäcklund reaction has been employed to prepare protected 2,3-disubstituted cyclopent-3-enones which have been converted into cyclopent-3- and -2-enones; the α-iodosulphone precursors were obtained by a double Michael approach using a three-component coupling sequence to introduce the alkyl substituents and this methodology has been used to develop a short synthetic route to the antimicrobial natural product, tetrahydrodicranenone B (**1**).

Substituted cyclopentenones are widespread in nature and considerable effort has been directed towards devising procedures for their preparation. We required a convergent approach to 2,3-disubstituted cyclopentenones which would provide access to both Δ^3- and Δ^2-isomers. We now report the successful realisation of this goal and illustrate the methodology with a short synthetic route to the antimicrobial natural product, tetrahydrodicranenone B(**1**).[1,2] The key synthetic step involves the facile (−78 °C, <1 h) Ramberg–Bäcklund reaction of α-iodosulphone (**8**). A related approach to cyclopentenones, recently published by Matsuyama *et al.*[3] is limited to monosubstituted derivatives and requires longer reaction times at room temperature or higher.

Scheme 1 illustrates the overall methodology. We recently reported[4] that 3-methyoxycarbonylthiin-4-one (**2**) undergoes conjugate addition with a range of organocopper reagents to give 2-substituted β-keto esters which, after alkylation and demethoxycarbonylation, give the corresponding 2,3-disubstituted compounds. The generality of this three-component coupling sequence was limited by the problems encountered with the demethoxycarbonylation reaction. These problems can be overcome by the use of allyl ester (**3**).† Treatment of compound (**3**) with butylmagnesium bromide/cat. $CuBr{\cdot}SMe_2$ gave the conjugate adduct (**4a**) which was alkylated to produce compound (**5a**). Decarboxyallylation was then efficiently achieved using $Pd(PPh_3)_4$–morpholine[5] to give sulphide (**6a**) in 87% yield as a *cis,trans* mixture. Oxidation to sulphone (**7a**) was followed by a second Michael sequence using Me_3SiI/ethylene glycol[6] to generate the Ramberg–Bäcklund precursor (**8a**). Treatment of α-iodosulphone (**8a**) with $KOBu^t$ at −78 °C produced the protected cyclopent-3-enone (**9a**) in 78% yield. Hydrolysis of compound (**9a**) using pyridinium tosylate[7] gave the Δ^3-enone (**10**); the use of HCl gave the Δ^2-isomer (**11**).

This methodology was applied to the synthesis of tetrahydrodicranenone B (**1**) in the following way. 3-Allyloxycarbonylthiin-4-one (**3**) was subjected to the 3-component coupling/Ramberg–Bäcklund sequence to give the requisite cyclopentene (**9b′**) in 6 steps (16% overall yield, unoptimised) as shown in Scheme 1 (series b). Hydrolysis of compound

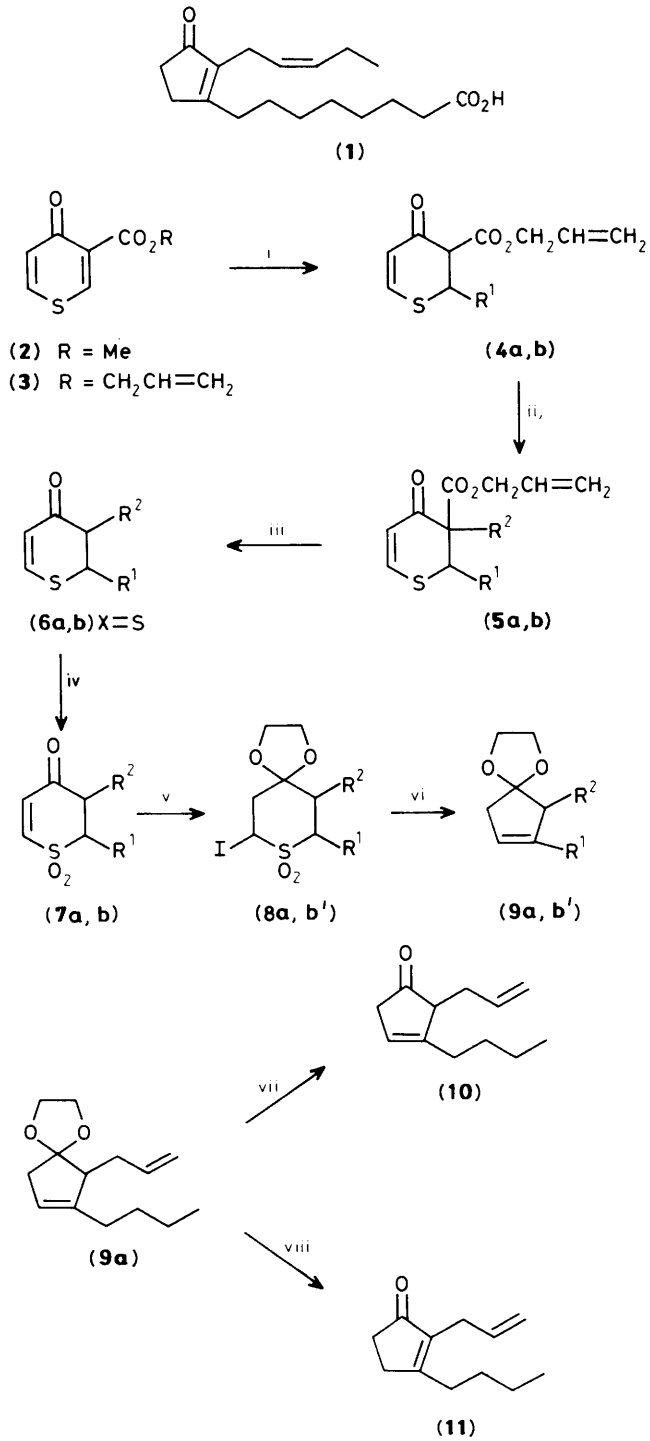
† All new compounds gave consistent spectral and analytical or mass spectrometric data.

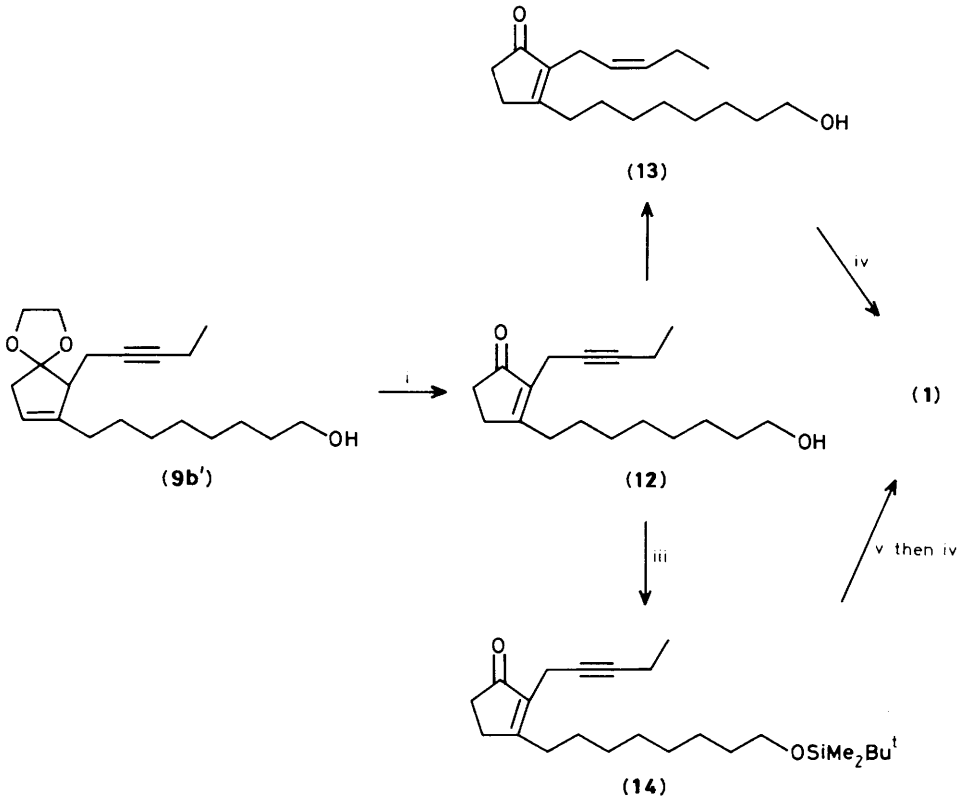
a; $R^1 = C_4H_9$, $R^2 = CH_2CH{=}CH_2$

b; $R^1 = (CH_2)_8OSiMe_2Bu^t$, $R^2 = CH_2C{\equiv}CCH_2Me$

b′; $R^1 = (CH_2)_8OH$, $R^2 = CH_2C{\equiv}CCH_2Me$

Scheme 1. *Reagents and conditions:* i, R^1MgBr, 2.5% $CuBr{\cdot}SMe_2$ (**a**, 64%; **b**, 60%); ii, NaH, R^2Br (**a**, 69%; **b**, 82%); iii, 5% $Pd(PPh_3)_4$–morpholine (**a**, 87%; **b**, 93%); iv, *m*-chloroperbenzoic acid (**a**, 84%; **b**, 83%); v, Me_3SiI, $HOCH_2CH_2OH$ (**a**, 69%; **b**, 65%); vi, $KOBu^t$, −78 °C, 30 min (**a**, 78%; **b**, 65%); vii, pyridinium tosylate, aq. acetone (78%); viii, 5% aq. HCl (81%).





Scheme 2. *Reagents:* i, 5% aq. HCl (95%); ii, H_2, 10% Pd–C (85%, containing impurities, see text); iii, Bu^tMe_2SiCl, Et_3N, 4-*N*,*N*-dimethylaminopyridine; iv, Pt, O_2;[2] v, H_2, Pd-$BaSO_4$ then H_3O^+.[2]

(**9b'**) with HCl produced the enone (**12**) which on catalytic hydrogenation gave the *Z*-alkene (**13**) contaminated by the corresponding *E*-isomer and over-reduced analogue, (Scheme 2). Alternatively, silylation of (**12**) gave (**14**) which has been reported[2] to undergo smooth, stereoselective alkyne reduction. Compounds (**13**) and (**14**) were spectroscopically identical to authentic samples which have been converted[2] into tetrahydrodicranenone B (**1**) in 1 and 3 steps, respectively.

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