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Diastereoselective ruthenium-catalysed cycloisomerisation of diallyllactones: preparation of *exo*-methylene spirolactones

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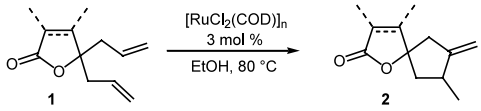
Abstract—Diallyllactones (obtained from cyclic anhydrides via a double allylation reaction promoted by titanium tetrachloride) were cycloisomerised using 5 mol% of cyclooctadienyl ruthenium dichloride in ethanol providing the corresponding exomethylene spirolactones in good yields, with moderated to good diastereomeric excess. © 2003 Elsevier Science Ltd. All rights reserved.

In recent years, increasing attention has been focused on structural modifications that feature restrictions in conformational flexibility in order to better attain optimal puckering. In this context, the preparation of spirobicyclic compounds are usually investigated to obtain the over mentioned restriction properties.[1] Among these, spirobicyclic lactones have not received great attention from a synthetic point of view. However, they have been recently proposed as mimics of the sugar moiety of nucleosides.[2] In this field, we recently described the preparation of novel spirolactones using a sequence involving allylation or alkylation of cyclic anhydrides followed by ring closing metathesis.[3] To increase the potentialities of the diallyl lactones, we decided to explore a metal catalysed cycloisomerisation in this series. Cycloisomerisation reactions of α,ω-dienes catalysed by organotransition metal complexes have recently attracted attention as a useful means for regiodefined carboannulation.[4] Transformations of this variety are attractive due to their intrinsic atom economy,[5] as well as the importance of the produced alkenes as synthetic intermediates. In this paper, we wish to describe a convenient ruthenium complex-catalysed procedure for the preparation of exomethylene spirolactones.[6]

Synthesis of diallyl lactones was achieved using the following route. Diallyllactones **1a**–**h** were synthesised by titanium tetrachloride promoted double allylation reaction of cyclic anhydrides with allyltrimethylsilane in a mixture of dichloromethane and nitromethane.[7] As an extension of our previous work, we started diallyllactone spirocyclisation using a ruthenium-based catalyst which has exhibited good activity and was recently reported by Itoh and co-workers.[8] Our investigation began with the cyclisation reaction on **1a**. First, the influence of the solvent and catalyst on conversion rates was examined, in order to obtain good yields of **2a**. As already observed by Itoh, the cyclisation reaction failed in the presence of a phosphine liganded ruthenium(II) complex, leaving unchanged starting materials. Chloroform, DMF and toluene were found to be inefficient while ethanol afforded low yields of spirolactone **2a**. Switching phosphine liganded ruthenium(II) to $[RuCl_2(COD)]_n$ and using ethanol as solvent yielded quantitative conversion in **2a** after 12 h. Attempts conducted over 40 h at 80°C led to a 70/30 mixture of **2a** and an isomer of **2a** in which the *exo* double bond had migrated in the cyclopentyl ring (Scheme 1).

Other diallyl lactones were engaged under similar conditions to determine the scope of the reaction.[9] The results are summarised in Table 1.

The diastereoselectivity was increased by the introduction of a double bond in the lactone cycle (entries 1–3) and by β-carbonyl substitution (entries 5 and 9). On the other part, cycloisomerisation reaction of diallyl δ-lactone **1g** failed and only the *trans*-esterification product **3a** with ethanol was obtained in 86% yield (Scheme 2). Moreover, we did not observe any cycloisomerisation



Scheme 1.

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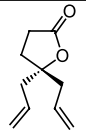
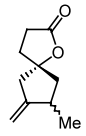
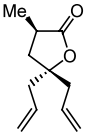
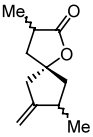
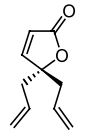
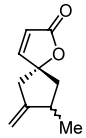
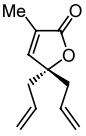
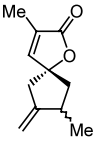
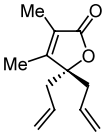
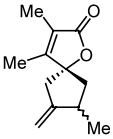
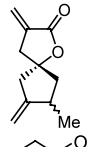
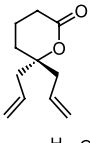
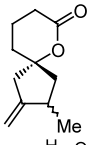
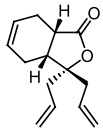
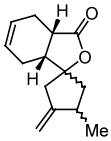
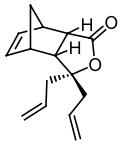
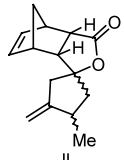
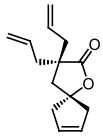
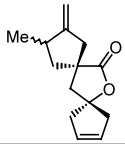
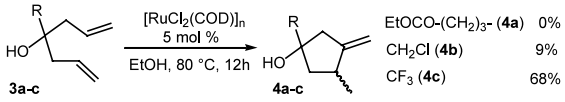
Table 1. Synthesis of spirolactones from cyclic anhydrides

Entry	Diallyl lactone		Spirolactone		Yield (%) d.r.
1		**1a**		**2a**	75 67/33[a]
2		**1b**		**2b**	92 47/36/9/8[a]
3		**1c**		**2c**	77 76/24[a]
4		**1d**		**2d**	78 75/25[a]
5[a]		**1e**		**2e**	83 95/5
6[b]		**1f**		**2f**	
7		**1g**		**2g**	0
8[c]		**1h**		**2h**	78 33/33/18/16
9[a]		**1i**		**2i**	74 56/27/9/8
10[x]		**5**		**6**	69 56/44[d]

a : Diastereoisomeric ratio determined by gas chromatography.
b : Spirolactone **2f** was found to be very unstable during its purification over silica gel.
c : Diastereoisomeric ratio determined by ^{13}C NMR.
d : Diastereoisomeric ratio determined by ^{1}H NMR.

products indicating the great influence of the hydroxy function on the reaction course. As a possible explanation, we think that the tertiary hydroxy function chelates the ruthenium atom making the oxidative insertion step impossible. In this context, we have examined the reaction of two other 4-hydroxyhepta-1,6-dienes substituted by an electron withdrawing group (**3b** and **3c**) in position 4.

The cycloisomerisation reaction of diene **3b** over 12 h afforded only very low conversion rate while the trifluoromethyl analog **3c** led to cyclised product **4c** in 68% yield.



Scheme 2.

The structures of the diallyl products and spirolactones were assigned based on IR, ^{1}H, ^{13}C NMR spectroscopic and mass spectrometric data. A NOESY NMR experiment conducted on **2c** allowed us to determine the stereochemistry of the major product which gave a cross peak between H2/H3 and H3/Me. A complementary NOESY NMR experiment conducted on the minor diastereoisomer confirmed a *trans* relationship between the methyl group and the lactone oxygen atom in the major product (Fig. 1).

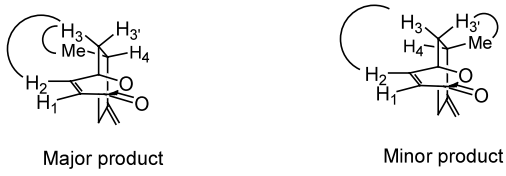
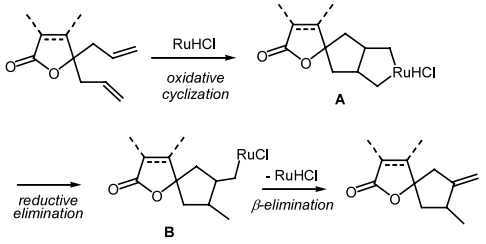


Figure 1.

The mechanism of the cycloisomerisation reaction can be explained by the postulated catalytic cycle defined by Itoh et al., in which the following three steps (oxidative cyclisation, reductive elimination and β-elimination) could be involved in the formation of spirolactones (Scheme 3).[10]

To understand the origins of the diastereoselectivity observed, we can postulate two possibilities. (1) the formation of the ruthenacyclopentane exhibits a *cis* junction and in this case the determining step is the oxidative insertion step. (2) the formation of the ruthenacyclopentane **A** exhibits a *trans* junction and in this case the determining step is the reductive elimination. In the first case, the ruthenium atom could be placed in *anti* or *syn* position. The *anti–cis* intermediate appears to be the more sterically hindered while the *syn–cis* would be certainly less sterically hindered and also certainly stabilised by the presence of oxygen atom (Fig. 2).



Scheme 3.

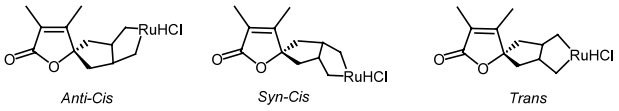


Figure 2.

Nevertheless, the observation of the major isomer that exhibits the methyl group and the oxygen atom in *anti* position deflects the reaction pathway via the *anti–cis* intermediate. So we turned our attention to the *trans* intermediate in which the diastereoselection does not occur in its formation but in the following reductive elimination step. By analogy of fused zirconacyclopentane where the junction was found to be *trans*,[11] the *trans* Ru intermediate could certainly be formed. The reductive step would give two Ru(II) (*cis* or *trans*) intermediates **B** (Scheme 3). Certainly for steric reasons, the *cis* isomer of **B** would be largely preferred; moreover the oxophillic ruthenium can chelate the lactone oxygen atom giving an increased stability to the Ru intermediate that leads to the major product.

In conclusion, with cyclooctadienyl ruthenium dichloride, diallyl lactones react via a cycloisomerisation reaction to provide selectively exomethylene spirolactones. Studies to improve diastereoselectivity are currently underway and will be reported in due course.

Acknowledgements

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9. **General procedure for the preparation of exomethylene spirolactone**: cyclooctadienyl ruthenium dichloride (5×10^{-2} mmol) was added to a diallyllactone (1 mmol) solution in ethanol (20 mL). The reaction mixture was then warmed to reflux during 12 h. After removal of the solvent, the crude product was purified by chromatography over silica gel (eluent: petroleum ether/ether (50/50)) to afford spirolactones **2**. Compound **2c** (major): ^{1}H NMR (400 MHz, $CDCl_3$): 1.14 (d, 3H, $J=6.7$ Hz, CH_3), 1.66 (dd, 1H, $J=13$, 13.3 Hz, CH_2), 2.00 (ddd, 1H, $J=13.3/7.2/2.3$ Hz, CH_2), 2.57 (bd, 1H, $J=17.7$ Hz, CH_2), 2.78 (dq, 1H, $J=17.7/2.3$ Hz, CH_2), 2.89–3.01 (m, 1H), 4.91 (q, 1H, $J=2.3$ Hz, $=CH_2$), 4.94 (q, 1H, $J=2.3$ Hz, $=CH_2$), 6.02 (d, 1H, $J=5.7$ Hz, =CH), 7.31 (d, 1H, $J=5.7$ Hz, =CH). ^{13}C NMR (100 MHz, $CDCl_3$): 17.8, 37.5, 42.6, 45.3, 93.9, 106.5, 120.7, 152.6, 158.6, 172.2. MS *m*/*z* (%): 164 ($M^{+\bullet}$, 24), 122 (17), 121 (12), 107 (10), 97 (12), 95 (10), 94 (29), 93 (50), 92 (29), 91 (24), 82 (41), 79 (46), 77 (27), 69 (11), 68 (70), 67 (58), 66 (18), 65 (21), 63 (10), 55 (20), 54 (64), 53 (44), 52 (13), 51 (27), 50 (13), 42 (18), 41 (56), 40 (36), 39 (100). Compound **2c** (minor): ^{1}H NMR (400 MHz, $CDCl_3$): 1.18 (d, 3H, $J=7.0$ Hz, CH_3), 1.78 (dd, 1H, $J=13.7/6.5$ Hz, CH_2), 2.21 (dd, 1H, $J=13.7/8.8$ Hz, CH_2), 2.68 (bs, 2H, CH_2), 2.73–2.77 (m, 1H), 4.91 (1H, overlapped with vinylic proton of major isomer, $=CH_2$), 4.95 (q, 1H, $J=2.2$ Hz, $=CH_2$), 5.97 (d, 1H, $J=5.6$ Hz, =CH), 7.38 (d, 1H, $J=5.6$ Hz, =CH). ^{13}C NMR (100 MHz, $CDCl_3$): 20.2, 36.8, 43.1, 43.6, 93.9, 107.2, 119.8, 152.7, 158.9, 172.3. MS *m*/*z* (%): 164 ($M^{\cdot+}$, 24), 122 (17), 121 (12), 107 (10), 97 (12), 95 (10), 94 (29), 93 (50), 92 (29), 91 (24), 82 (41), 79 (46), 77 (27), 69 (11), 68 (70), 67 (58), 66 (18), 65 (21), 63 (10), 55 (20), 54 (64), 53 (44), 52 (13), 51 (27), 50 (13), 42 (18), 41 (56), 40 (36), 39 (100).
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