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Efficient assembly of α-methylene-γ-butyrolactones via a novel, tandem Claisen–ene rearrangement

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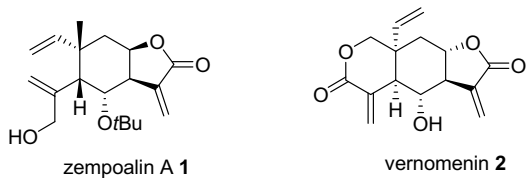
Abstract—A novel method for the rapid assembly of α-methylene-γ-butyrolactones, using a tandem Claisen–ene rearrangement as a key step, is presented. The importance of the structure of the Lewis acid promoters and the mechanism of action of Et_2AlSPh are discussed.

α-Methylene-γ-butyrolactones are ubiquitous subunits in a wide variety of biologically active natural products.[1] In particular, there are numerous examples in which the γ-butyrolactone fragment is part of a more complex ring system, such as in zempoalin A **1**[2] and vernomenin **2**[3] (Fig. 1). The widespread occurrence of γ-butyrolactones has stimulated the emergence of many elegant methods for their efficient construction.[4]

As part of an ongoing research programme, aimed at the rapid and flexible synthesis of some of these naturally occurring compounds, we have recently reported complementary methodologies for the assembly of substituted α-methylene-γ-butyrolactones.[5] Our strategies rested upon an initial ene reaction[6] between a variety of aldehydes **3** and the functionalised allylsilane **4**, affording the (*Z*)-homoallylic alcohols **5**, followed by their subsequent transformation into the desired products **9**, according to the protocol depicted in Figure 2.



zempoalin A **1** vernomenin **2**

Figure 1. Selected natural products.

In an antithetic sense, our disconnection of α-methylene-γ-butyrolactones involves the concomitant cleavage of the O1–C2 and C4–C5 bonds of **9**, leading directly to aldehyde **3** and allylsilane **4**. Closer examination of the structures of zempoalin A **1** and vernomenin **2** revealed the presence, in both natural products, of a four carbon side chain connected at C5 of the lactone residue and bearing γ,δ-unsaturation. Application of the above-mentioned retron to **10** generates the annelating agent **4** and the unsaturated aldehyde **11**, which can be obtained by a Claisen rearrangement[7] of the allyl vinyl ether **12**, itself readily available from the corresponding allylic alcohol **13** (Fig. 3).

Although a variety of Lewis acids are known to catalyse efficiently the carbonyl–ene[8] or the Claisen[9] rearrangement, to the best of our knowledge, only one example of a copper-complex that promotes both reactions simultaneously has been reported.[10] Therefore, the establishment of a tandem Claisen–ene process that would lead in a single operation to the unsaturated adducts **10**, might be a useful addition to the methods currently available in organic synthesis.

Accordingly, several allyl vinyl ethers were prepared from the corresponding allylic alcohols[11] and treated with a variety of Lewis acids. Extensive screening experiments revealed that only one catalyst, Et_2AlSPh,[12] efficiently promoted the Claisen rearrangement of **14**, affording the desired aldehyde **15** in 80% yield (Fig. 4).

Unfortunately, Et_2AlSPh did not catalyse the subsequent ene reaction. In stark contrast, Et_2AlCl promoted

Keywords: Claisen rearrangement; Ene reaction; α-Methylene-γ-butyrolactones; Tandem reaction; Lewis acid.
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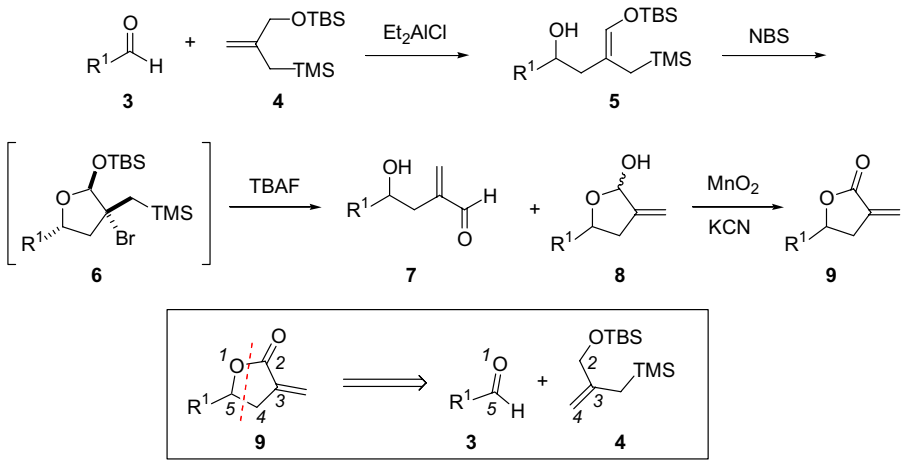


Figure 2. Connective synthesis of α-methylene-γ-butyrolactones.

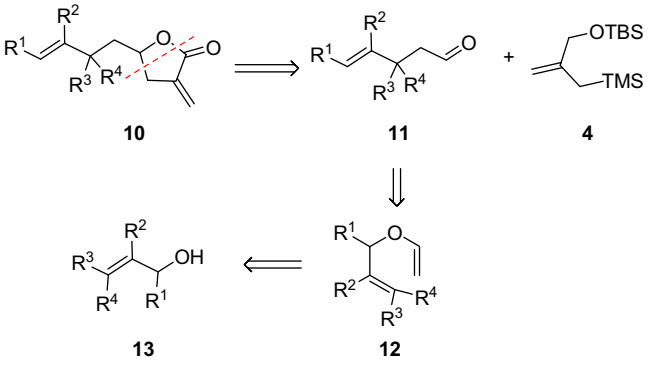


Figure 3. Retrosynthetic analysis.

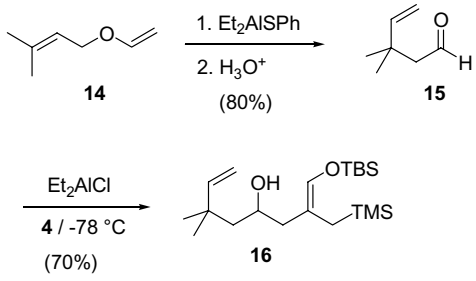


Figure 4. Testing the Lewis acids.

the condensation of **15** with allylsilane **4**, but was completely inert towards the Claisen rearrangement. Such a dichotomous behaviour, displayed by two closely related Lewis acids, was puzzling and the Claisen rearrangement of **14**, catalysed by Et_2AlSPh, was carefully reinvestigated. Much to our surprise, and though the starting material **14** rapidly disappeared, no aldehyde could be observed in the crude reaction mixture *before work-up*. However, *after* aqueous acidic treatment, **15** was produced in high yield. This experiment strongly suggested that a stable intermediate, generated under these reaction conditions, was subsequently transformed into the desired aldehyde **15** *upon work-up*. Spectroscopic analysis of the crude product revealed this intermediate to be *O*,*S*-aluminium acetal **17**.[13] The inability of Et_2AlSPh to catalyse the ene reaction can now be fully understood. Indeed, after promoting the Claisen rearrangement of the allylvinyl ether **14**, this Lewis acid rapidly reacts with the in situ generated aldehyde **15**, forming the corresponding *O*,*S*-aluminium acetal **17**, which is inert towards allylsilane **4** (Fig. 5).

It thus transpires that, in order to successfully realise the desired tandem Claisen–ene rearrangement, it is imperative to regenerate aldehyde **15** from the tetrahedral intermediate **17**, before the addition of the ene partner **4**. Gratifyingly, this transformation could be efficiently achieved by adding PhSCl to *O*,*S*-aluminium acetal **17**.

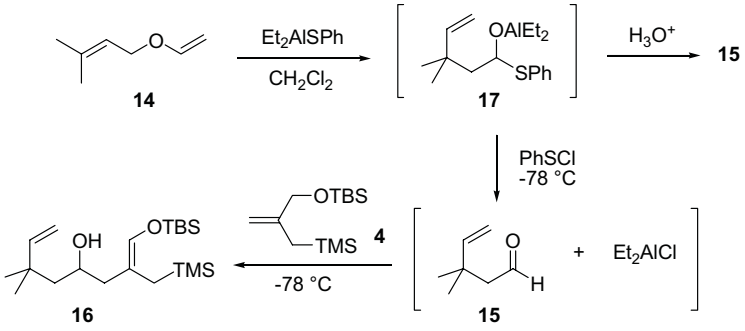
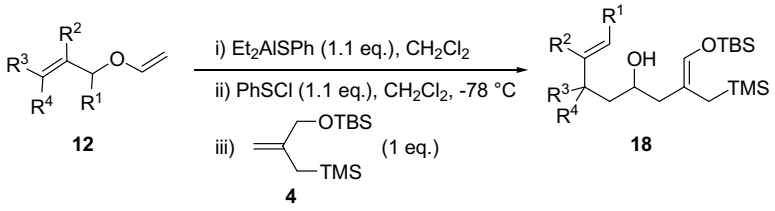


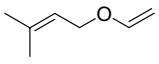
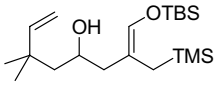
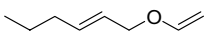
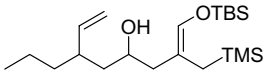
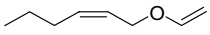
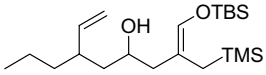
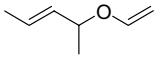
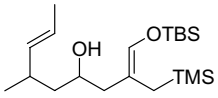
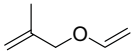
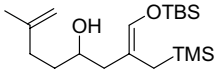
Figure 5. One-pot Claisen–ene rearrangement.

Interestingly, Et_2AlCl, the most competent catalyst for the ene reaction, is co-produced at the same time. The long sought—after homoallylic alcohol **16** can now be obtained in a single operation, by initially treating the allyl vinyl ether **14** with Et_2AlSPh, followed by the addition of PhSCl and, after a few minutes, of allylsilane **4**. Some selected examples of this novel tandem Claisen–ene methodology are displayed in Table 1.

As can be seen from Table 1, a variety of substituted allyl vinyl ethers **12** smoothly undergo the desired sequence of reactions, affording the corresponding adducts **18** (Table 1, entries 1–4) in good overall yields. Surprisingly, Claisen rearrangement of methallyl vinyl ether does not occur under these conditions (Table 1, entry 5). Whilst most of these transformations can be performed at room temperature, it is sometimes

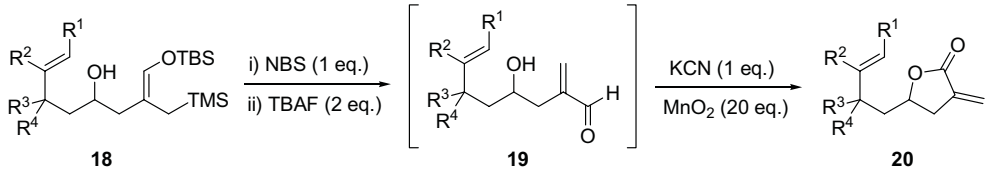
Table 1. Tandem Claisen–ene transformation of allylvinyl ether **12**

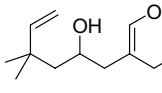
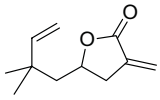
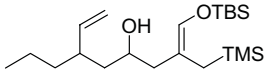
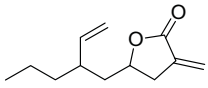
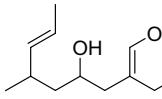
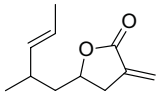


Entry	Substrate	Product	Yields (%)[a]
1			51[b]
2			54[b]
3			50[c]
4			48 [c]
5			0[b]

[a] All yields are for pure, isolated products.
[b] Claisen rearrangement performed at rt.
[c] Claisen rearrangement performed at reflux.

Table 2. Formation of the corresponding α-methylene-γ-butyrolactones **20**



Entry	Substrate	Product	Yields (%)[a]
1			63
2			59
3			51

[a] Overall yields for the three steps, two operations sequence and refer to pure, isolated products.

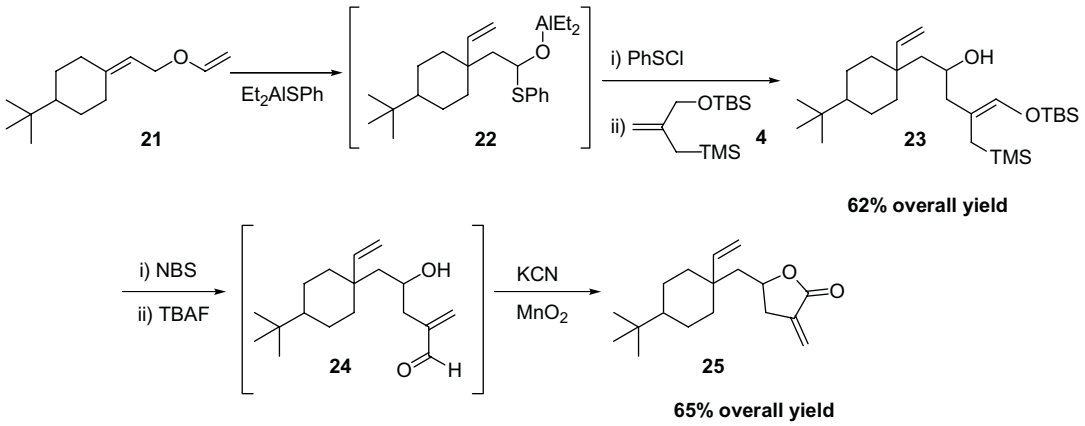


Figure 6. Application to a model synthesis.

necessary to carry out the Claisen rearrangement at a higher temperature (Table 1, entries 3 and 4). In all cases, the decomposition of the tetrahedral intermediate occurs quantitatively at −78 °C, upon addition of PhSCl.

The ω-unsaturated homoallylic ethers **18** thus obtained were converted into the corresponding α-methylene-γ-butyrolactones **20** in good overall yields (Table 2).

This three step, two operations protocol is performed without isolation of the intermediate β′-hydroxy enal **19**. A single chromatographic purification, at the end of this sequence, is sufficient to produce analytically pure **20**.

To illustrate the power of this approach, the simplified model of the zempoalin A **1** and vernomenin **2** middle core **25** was readily assembled (Fig. 6).

The Claisen rearrangement of vinyl ether **21**, promoted by Et_2AlSPh, smoothly afforded the tetrahedral intermediate **22**, which upon treatment with PhSCl at −78 °C, decomposed into the corresponding aldehyde and Et_2AlCl. Addition of the allylsilane **4** to the reaction mixture led to the formation of the ene adduct **23** in 62% overall yield. The subsequent transformation of **23** into α-methylene-γ-butyrolactone **25** proceeded in 65% overall yield.

In summary, we have developed a novel tandem Claisen–ene rearrangement protocol that affords a variety of substituted homoallylic alcohols in good yields. These adducts are useful intermediates in the preparation of functionalised α-methylene-γ-butyrolactones. The mechanism of Et_2AlSPh-catalysed Claisen rearrangement has been investigated and the participation of a unique *O*,*S*-aluminium acetal has been demonstrated. Finally, the synthetic utility of this novel methodology has been illustrated by the rapid assembly of a variety of α-methylene-γ-butyrolactones.[14] Further work is now directed towards broadening the scope of this method and applying it to the total synthesis of zempoalin A **1** and vernomenin **2**. The results of these investigations will be reported in due course.

Acknowledgements

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1992, 255–265; (c) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.
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8. A number of Lewis acid promoters have been developed, such as $BF_3{\cdot}Et_2O$, $AlCl_3$, $SnCl_4$, $TiCl_4$ and alkylaluminium halides (R_nAlX_{3-n}). For some selected recent applications, see: $SnCl_4$: (a) Mikami, K.; Sakuda, S. *J. Chem. Soc., Chem. Commun.* **1993**, 710–712; (b) Tomioka, K.; Masumi, F.; Yamashita, T.; Koga, K. *Tetrahedron* **1989**, *45*, 643–650; (a) Me_2AlCl: Nagasawa, T.; Kitamura, M.; Suzuki, K. *Synlett* **1995**, 1183–1186; (b) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 2165–2168; $EtAlCl_2$: Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538–4545; Et_2AlCl: Hiroi, K.; Yamamoto, M.; Kurihara, Y.; Yonezawa, H. *Tetrahedron Lett.* **1990**, *31*, 2619–2622.
9. A large number of catalysts for the Claisen rearrangement have been reported, including BCl_3, Et_2AlSPh, R_2AlCl, Hg(II), Pd(II) and trialkylaluminium species. For some selected recent applications, see: (a) Akiyama, K.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 7217–7220; (b) Tayama, E.; Saito, A.; Ooi, T.; Maruoka, K. *Tetrahedron* **2002**, *58*, 8307–8312; (c) Hiersemann, M. *Synlett* **1999**, 1823–1825; (d) Maruoka, K.; Banno, H.; Nonoshita, K.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 1265–1266.
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13. ^{1}NMR shifts: in the aldehyde, $\delta_H = 9.75$–9.95 ppm (t), in the *O–S* acetal, $\delta_H = 5.15$–5.35 ppm (m), in the ene adduct, $\delta_H = 3.65$–3.85 ppm (m).
14. *Typical experimental procedure:* To neat thiophenol (0.283 g, 2.55 mmol) was added dropwise 2.55 ml of triethylaluminium (1 M solution in hexanes, 2.55 mmol). The mixture was stirred at 25 °C for 30 min. To a solution of 0.26 g of allylvinylether **14** (Fig. 5, 2.32 mmol) in 30 ml of CH_2Cl_2, the freshly prepared solution of Et_2AlSPh was added dropwise. This mixture was stirred at 25 °C for 30 min and then cooled at −78 °C. To this cooled mixture was added dropwise and successively 0.37 g of PhSCl and 0.7 g of allylsilane **4** (Fig. 5, 86% pure, 2.33 mmol). The mixture was stirred at −78 °C for 2 h, then 30 ml of a saturated solution of $NaHCO_3$ was added and the mixture was allowed to warm up to rt. The aqueous layer was extracted with CH_2Cl_2 (3×40 ml). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue over silica gel (eluted with EtOAc–petroleum ether, 1:40) gave 439 mg (51%) of pure ene adduct **16**. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 6.06 (1H, s), 5.90 (1H, dd, $J = 17.4$, 10.8 Hz), 4.97 (1H, dd, $J = 17.7$, 1.2 Hz), 4.95 (1H, dd, $J = 10.5$, 0.9 Hz), 1.92 (1H, dd, $J = 13.8$, 4.2 Hz), 1.81 (1H, dd, $J = 13.8$, 8.7 Hz), 1.67 (1H, d, $J = 13.5$ Hz), 1.46 (1H, dd, $J = 14.1$, 7.8 Hz), 1.39 (1H, dd, $J = 14.4$, 3.3 Hz), 1.26 (1H, d, $J = 13.2$ Hz), 1.07 (3H, s), 1.06 (3H, s), 0.91 (9H, s), 0.10 (6H, s), 0.01 (9H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 149.14, 134.68, 115.37, 110.70, 66.04, 49.80, 43.48, 36.58, 27.77, 26.00, 18.41, 17.54, −0.40, −4.93. MS (EI) *m/z*: 371 ($MH^{+\cdot}$, 1), 370 ($M^{+\cdot}$, 2). IR (film): 3397, 2956–2858, 1662, 1638, 1472, 1412, 1362, 1249, 1098, 1003, 838 cm^{-1}. Anal. Calcd for $C_{20}H_{42}O_2Si_2$ (370.7): C, 64.80; H, 11.42. Found: C, 65.26; H, 11.46.