An Efficient Stereoselective Synthesis of Substituted 1,3-Dienes

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Abstract: A stereoselective synthesis of substituted 1,3-dienes has been developed which utilises an Ireland–Claisen rearrangement/silicon-mediated fragmentation sequence. This sequence has been designed to introduce remote centres of asymmetry as well as stereodefined diene systems, and its application to an aziridine system is also described.

Key words: aziridine, Ireland–Claisen rearrangement, Sharpless asymmetric epoxidation, silicon-mediated fragmentation

Stereodefined 1,3-dienes are useful synthetic building blocks in organic synthesis[2] and their use in cycloaddition reactions has been of paramount importance in modern synthetic chemistry.[3,4] Although many methods exist for the synthesis of 1,3-dienes, even more efficient, and selective syntheses of dienes are still required. The synthesis of stereodefined enantiopure dienes still remains a challenge and the use of the aforementioned dienes in the Diels–Alder reaction increases molecular complexity and its stance in total synthesis is well documented.[5]

We have reported a synthesis of the Prelog–Djerassi lactonic acid and an approach to galbonolide B using an Ireland–Claisen rearrangement/silicon-mediated fragmentation sequence.[6] We now report a variant on this methodology which can be used to make stereodefined 1,3-dienes serving as a model for the construction of the C-C unit of rapamycin. We also report an application of this method for the construction of dienyl amines from a substituted aziridine. Allylic alcohols **1**, obtained from reduction of the corresponding esters with di-*iso*-butyl aluminium hydride, were epoxidised using the Sharpless asymmetric epoxidation method[7] to give the epoxy alcohols **2** in a good yield and with high enantiomeric purity. Oxidation of the epoxy alcohols **2** to the corresponding aldehydes **3** using the Swern procedure[8] was unsatisfactory; the Parikh–Doering oxidation,[9] however, proved to be highly successful. The reaction was complete within 10–30 minutes at 0 °C and the crude products were pure enough to be used in the subsequent steps. Nucleophilic addition of 2-lithioethenyl-trimethylsilane to the epoxy aldehydes **3** was performed at –110 °C to ensure that the epoxide moiety remained intact.[10] It is noteworthy that the nucleophilic addition of 2-lithioethenyl-trimethylsilane to the epoxy aldehydes **3** gives Cram products, as the reaction is directly influenced by the substituents on the oxirane ring.[11] A five-membered transition state assisted by a lithium cation binding to an aldehydic oxygen could be a useful model to predict the pathway of the incoming nucleophile. The approaching nucleophile could differentiate the two diastereotopic faces of the aldehyde due to the Burzi–Dunitz angle of attack (Figure 1).

The resulting diastereomers **5** and **6** were readily separated using conventional column chromatography.[12] The esterification of the diastereomeric alcohols **5** and **6** was quantitatively undertaken with propanoyl chloride in the presence of pyridine and 4-dimethylaminopyridine (Scheme 1).

With the two diastereomerically pure esters **7** and **8** in hand, the stage was set to investigate the Ireland–Claisen rearrangement.[13] Thus, the ester enolate of **8a** generated with lithium diisopropylamide (LDA) was trapped by trimethylsilyl chloride at –78 °C; the resulting silyl enol ether was subsequently allowed to reach room temperature. When the reaction mixture was monitored by thin layer chromatography, one non-polar product was prominent. The isolated product showed that a more favoured

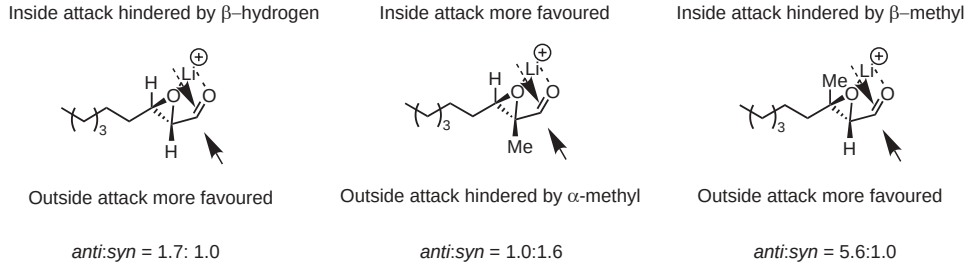

Figure 1 Nucleophilic addition to epoxy aldehydes

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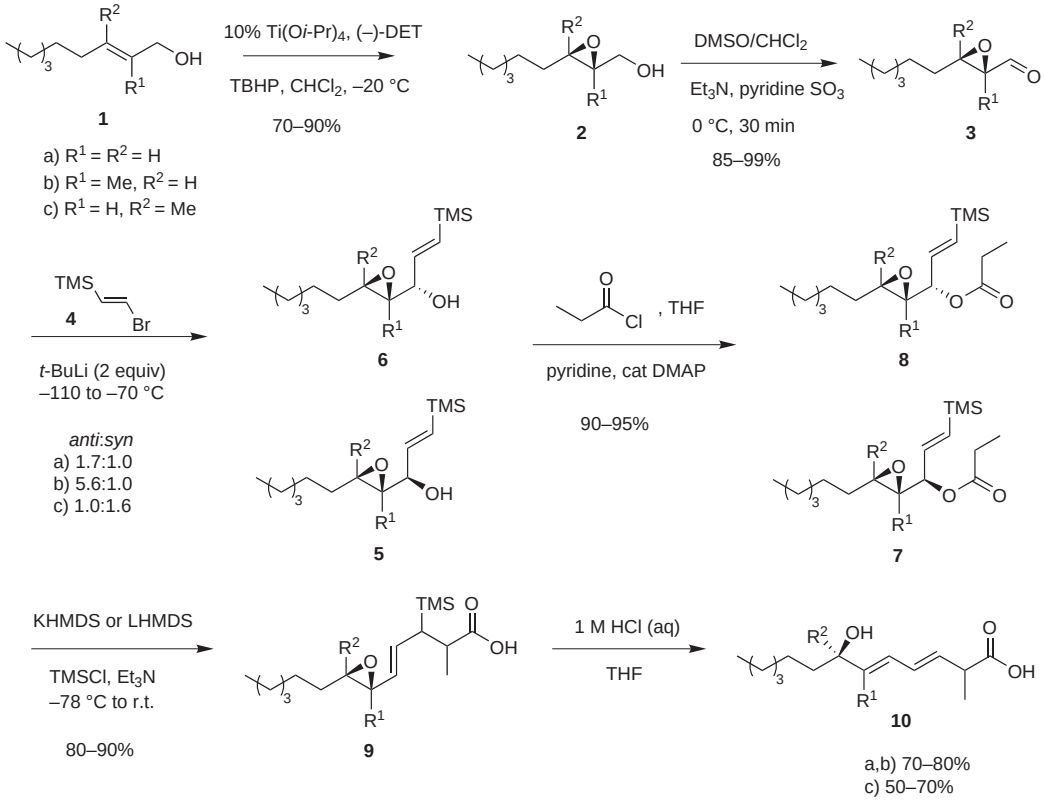
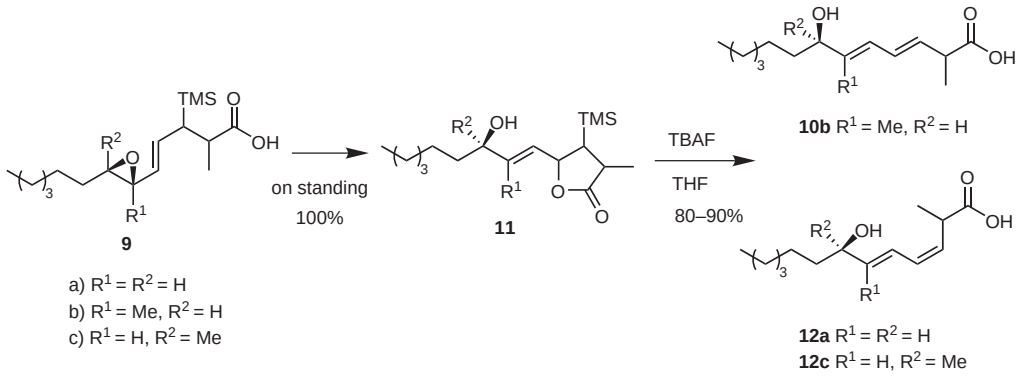


Scheme 1

base-promoted isomerisation of epoxide had occurred instead of the desired ester enolate rearrangement.[14] Attempts to prevent this unwanted isomerisation were made without much success. Using one equivalent of LDA, lowering reaction temperature down to –110 °C, premixing the substrate with trimethylsilyl chloride, and using *tert*-butyldimethylsilyl triflate as a trapping agent, all failed to induce the rearrangement. Incorporation of a dipolar co-solvent such as hexamethylphosphoric triamide (HMPA) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) had no effect on this particularly facile isomerisation. After screening other literature conditions, we were delighted to find the rearranged product **9** when the substrate **8a** was treated with LDA at –100 °C for 2–3 hours and then the resulting enolate was captured by a mixture of TMSCl–Et$_3$N (5 equiv:5 equiv).[15] It was rather unfortunate to find out that the reaction did not proceed via a chair-like transition state, as there was virtually no selectivity with or without the co-solvent HMPA. It is conceivable that a lone pair of electrons of the oxygen of the epoxide hinders the formation of a chair-like transition state by coordinating with lithium and neighbouring oxygen. Intercepting the lone pair electrons of the oxygen of the epoxide with a Lewis acid to direct the formation of a chair-like transition state was studied by using oxyphilic titanium tetraisopropoxide, as it was safely employed during the Sharpless asymmetric epoxidation. To our disappointment the reaction suffered from direct lithiation of the epoxide as previously experienced to give the dienyl alcohol **8d** resulting from a hydride transfer.[16] Alternative reaction conditions were sought to prevent the competing base-promoted isomerisation of the epoxide. The use of sodium-based bases such as sodium hydride and sodium *bis*(trimethylsilyl)amide were investigated in order to prevent both the direct lithiation of the epoxide and the epoxide oxygen chelation. However, the desired transformation was not observed.

The breakthrough on the Ireland–Claisen rearrangement was realised when either potassium *bis*(trimethylsilyl)amide or lithium *bis*(trimethylsilyl)amide was used in combination with a mixture of TMSCl–Et$_3$N. Modest stereoselectivity at the α methyl carbon was observed when KHMDS was used as the base (3.4:1), whereas LHMDS did not show any selectivity with or without the addition of HMPA. In the absence of HMPA or DMPU, chemical yields were improved and it is plausible that the epoxide oxygen could interact with the trimethylsilyl group of the silyl enol ethers. With the silicon-mediated fragmentation precursor **9** in hand a selective epoxide opening was investigated under acidic conditions.[6] The fragmentation was readily achieved using aqueous 1 M hydrochloric acid or 10% sulfuric acid solution in THF. The use of a Lewis acid to initiate fragmentation turned out to be a very destructive option at elevated temperature. One equivalent of boron trifluoride etherate gave the dehydrated product **9d** as the main product;[17] therefore the reaction was carried out at –78 °C with BF$_3$·OEt$_2$ catalysis. The allylsilanes **9a** and **9b** underwent fragmentation smoothly under Lewis acidic conditions. However, in the case of the β-methyl epoxy allylsilane **9c**, an unidentified product was observed with diminished yield of the *E*,*E*-diene **10c**.



9

a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = H$, $R^2 = Me$

11

Scheme 2

It is possible that the epoxide opening under acidic conditions competes to generate a tertiary carbocation as well as the allylic carbocation species.

The synthesis of the *E*,*Z*-dienes **12** was also exploited as the lactonised product **11** was obtained upon standing the hydroxy acids **9** at low temperature. The stereodefined *E*,*Z*-dienes **12** were isolated in excellent yield by fragmentation of the lactones **11** with tetrabutylammonium fluoride. The basic character of TBAF seemed to be responsible for the isomerisation. In the case of the trisubstituted alkene **11b**, the isomerisation did not occur, therefore the *E*,*E*-diene **10b** was obtained. Exposure of the lactones **11** to acid afforded a mixture of dienes **10** and **12** (Scheme 2).

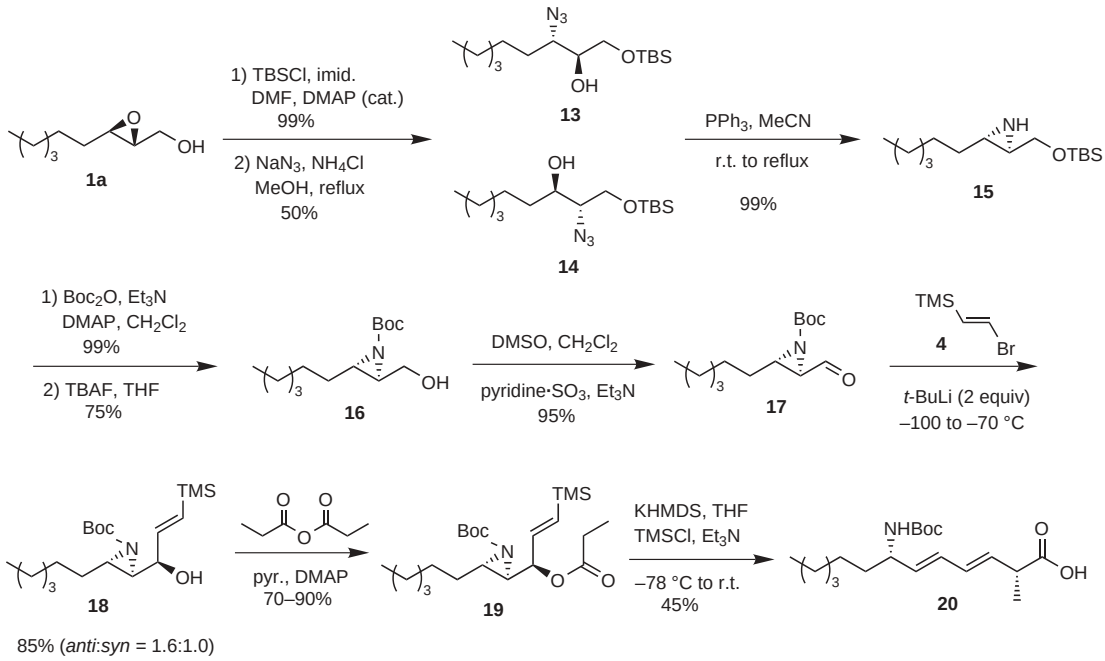
To conclude our studies on the generalised stereoselective synthesis of substituted dienes we had to address an unanswered question concerning the poor stereochemical outcome of the Ireland–Claisen rearrangement. It was reasoned that the tight chelation between the silicon of the silyl enol ether and the epoxide oxygen would inhibit the chair-like transition state as some non-chair transition state models have been suggested in certain bicyclic systems.[12] In order to test this plausible explanation, it was decided to prepare a three-membered ring model system, whose lone pair electrons were no longer available for chelation. The known epoxy alcohol **1a** was protected as its TBS silyl ether and treated with sodium azide to give the two chromatographically separable azido alcohols **13** and **14** in good overall yield. The resulting azido alcohols **13** and **14** were converted into the aziridine **15** by the Staudinger reduction protocol in excellent yield.[18] Protection of the aziridine **15** as its *t*-butyl carbonate and subsequent deprotection of the silyl ether gave the alcohol **16**. Parikh–Doering oxidation of **16** followed by the addition of the lithiated alkenylsilane of **4** to the resulting aldehyde **17** gave the Cram products **18** and its diastereomer with expected selectivity (*anti*:*syn* = 1.6:1.0). However, to our surprise, the subsequent esterification turned out to be troublesome as the aziridine ring was opened by chloride anion.[19] Ring closure of **19a** was partially successful under basic conditions[20] and the ring-opening in the esterification step was avoided by using propionic anhydride instead of propionyl chloride (Scheme 3).

With the precursor **19** in hand, our optimised conditions for the Ireland–Claisen rearrangement were tested.[21] To our delight the isolated product **20** had undergone a rearrangement/silicon-mediated fragmentation cascade and existed as a single diastereomer, resulting from a chair transition state in the rearrangement step. Although the acid **20** was isolated in modest yield, we believe that the cascade reaction observed will be of significant synthetic use. Aziridine opening by chloride anion after rearrangement has depressed the yield of the final product and work is now in progress to prevent this undesired reaction.

In conclusion, we have extended our existing methodology to synthesise substituted dienes. The reaction sequence is efficient and simple enough to prepare the stereodefined dienes, *E*,*E* or *E*,*Z* and its application towards natural products will be reported in due course.

General Procedure for the Ireland–Claisen Rearrangement.
To a stirred solution of the propionate ester (6.4 mmol) in THF (50 mL) at –78 °C was added KHMDS (31.9 mmol in toluene). The yellow solution was stirred at –78 °C for 20 min and then a mixture of TMSCl–Et_3N (64.0 mmol/31.9 mmol) in THF (10 mL) was added. After stirring for 10 min at –78 °C the reaction mixture was allowed to warm up to r.t. and was stirred for a further 2 h. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O (3 × 25 mL). The combined organic extract was dried ($MgSO_4$), filtered and concentrated to yield the required acids, which were purified by flash column chromatography (Et_2O–petroleum ether 40:60).

(3*E*,5*E*)-(2*S*,7*S*)-7-*tert*-Butoxycorbonylamino-2-methyltrideca-3,5-dienoic Acid (20)
TLC (50% Et_2O–50% petroleum ether): R_f = 0.19; $[\alpha]_D^{25}$ +3.1 (*c* 0.65 in CH_3Cl). IR (thin film): ν_{max} = 3341 (br m, NH), 2930 and 2858 (s, C-H), 1710 (s, carboxylic C=O), 1513 (m) cm^{-1}. ^1H NMR: (500 MHz, $CDCl_3$): δ = 8.20 [1 H, br s, COOH], 6.13 (2 H, m), 5.74 (1 H, m), 5.57 (1 H, m), 4.55 (1 H, br s), 4.10 (1 H, br s), 3.20 (1 H, p, 7.1 Hz), 1.50–1.28 (19 H, m) and 0.89 (3 H, t, 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = rotamer: 180.7, 180.2 (C=O), 155.6, 157.8 (C), 134.8, 134.5 (CH), 131.6, 131.7 (CH), 131.4, 131.2 (CH), 129.5, 129.3 (CH), 81.1, 79.7 (Boc-CMe_3), 52.2, 53.5 (CH), 43.0 (CH), 35.7, 34.7 (CH_2), 32.1 (CH_2), 29.4, 29.3 (CH_2), 28.7, 28.6 (CH_2), 26.0 (CH_3), 22.9 (CH_2), 17.3 (CH_3) and 14.5 (CH_3). HRMS: 679.4887, ([MMH]$^+$, $C_{38}H_{67}N_2O_8$ requires 679.4892).



Scheme 3

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(13) A single crystal of **6a** of 3,5-dinitrobenzoyl derivative was obtained and the selectivity of **5b** and **6b** were made from analogy of our Galbonolide study.
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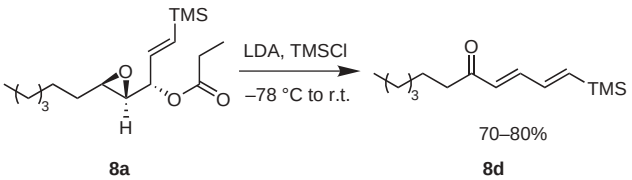

Scheme 4

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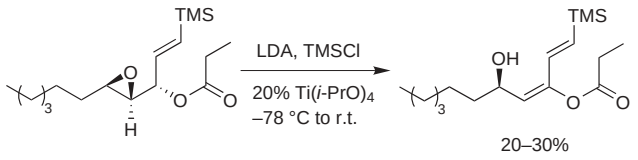
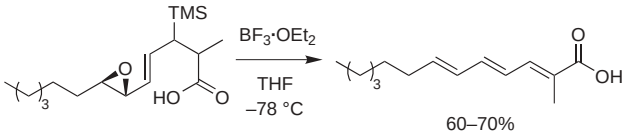
(16) Stereoselective epoxide opening using Ti(*i*-PrO)$_4$ (Scheme 5).



8a **8e**

Scheme 5

(17) $BF_3{\cdot}OEt_2$ initiated fragmentation of **9a** followed by dehydration of **10a** to give **9d** (Scheme 6).

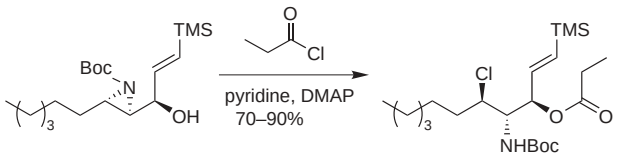


9a **9d**

Scheme 6

(18) (a) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962. (b) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (c) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 1. (d) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 16.

(19) Aziridine opening by chloride anion in esterification conditions (Scheme 7).



19 **19a**

Scheme 7

(20) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1998**, *63*, 3458.

(21) Conditions using LHMDS and TMSCl–Et_3N did not yield any identifiable product.