Pergamon

Tetrahedron Letters 39 (1998) 4373–4376

TETRAHEDRON LETTERS

Diastereoselective Fe(III) Mediated Oxidative Cyclisation Reactions of Cyclopropanone Acetals

Kevin I. Booker-Milburn*[a], Andy Barker[b] and Wayne Brailsford[a]

[a]School of Chemical Sciences, University of East Anglia, Norwich, Norfolk, England, NR4 7TJ, UK

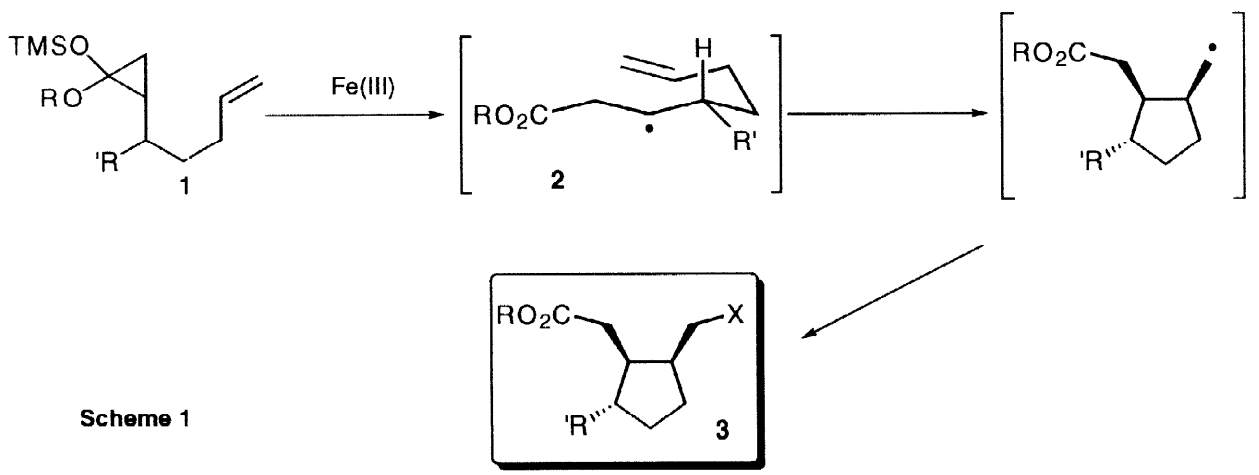
Fax: 01603 592015; e-mail: K.Booker-Milburn@uea.ac.uk

[b]Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, England, SK10 4TG

Received 21 March 1998; accepted 31 March 1998

Abstract: *Substituted cyclopropanone acetal derivatives undergo facile Fe(III) mediated oxidative cyclisation to the corresponding trisubstituted cyclopentane esters in good yield and with diastereoselectivities as high as 23:1.*

As part of a programme aimed at investigating the development of non-tin methods for radical generation we have reported that both cyclopropyl ethers[1] and cyclopropanone acetals[2] serve as good substrates for the Fe(III) mediated generation and cyclisation of carbon centred radicals. In the present study we report on the stereochemical influence exerted by a variety of substituents during the oxidative radical cyclisation of substituted cyclopropanone acetals to cyclopentane esters (**1**→**3**, Scheme 1). According to the comprehensive body of work compiled by Beckwith[3] such 5-*exo* radical cyclisations should proceed *via* the chairlike transition state **2** where the 2-substituent (R') adopts a pseudoequatorial position. This then leads to cyclopentane formation whereby the cyclised product (**3**) will, in principle, be formed with the stereochemistry as shown in Scheme 1.

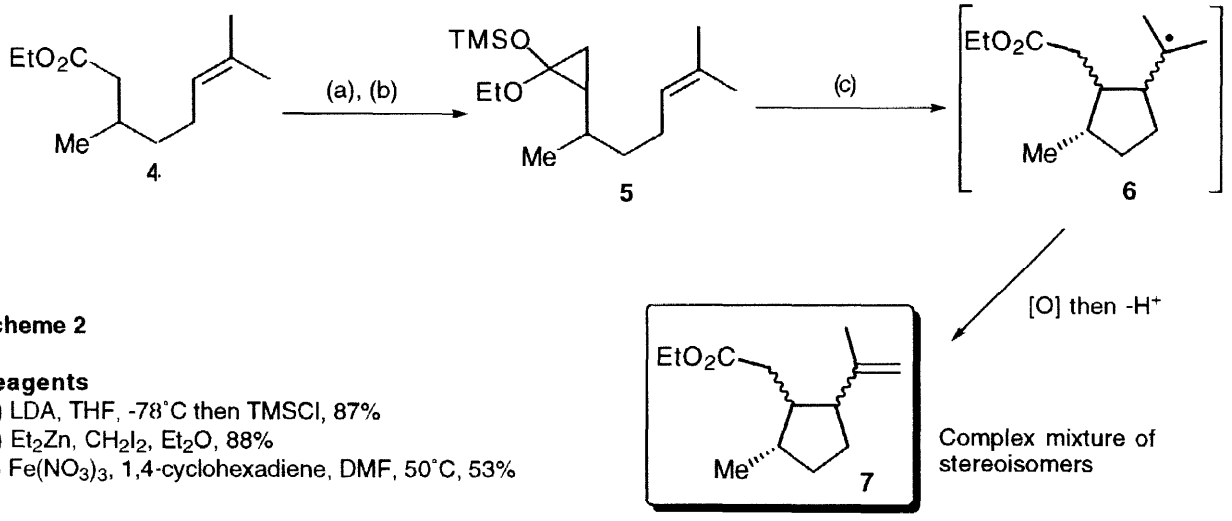


Scheme 1

Initially we elected to study the effect of a methyl group on the cyclisation. Treatment of (±)-ethyl citronellate **4** with LDA followed by quenching with TMSCl and anhydrous workup gave the corresponding labile

0040-4039/98/$19.00
PII: S0040-4039(98)00704-7

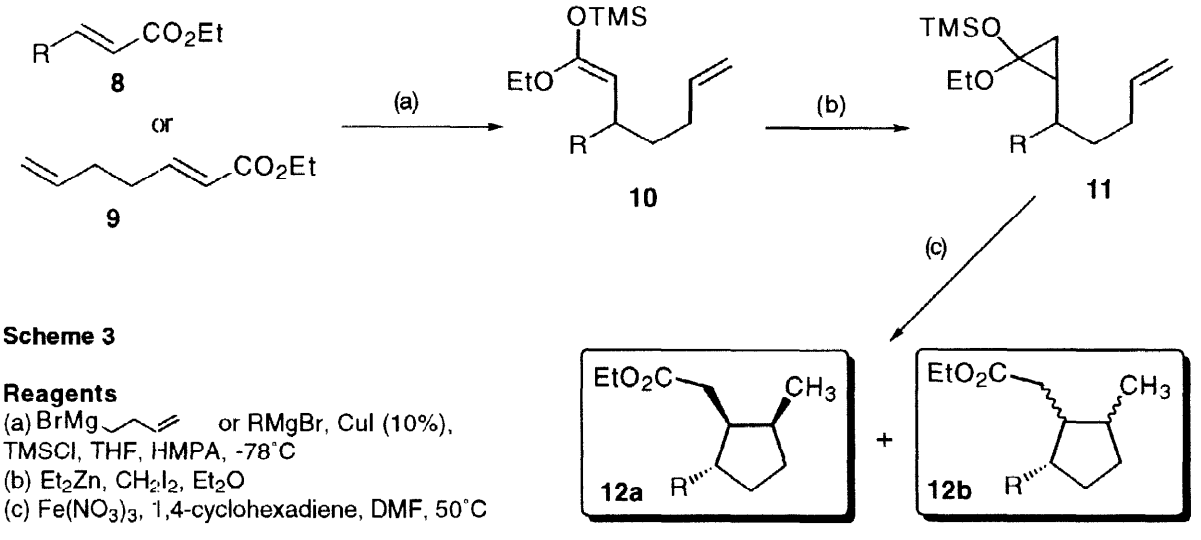
ketene-acetal which upon cyclopropanation gave an excellent yield of the stable cyclopropanone acetal **5**. Oxidative cyclisation of **5** under our usual conditions using ferric nitrate and 1,4-cyclohexadiene as a hydrogen atom donor[2] gave the cyclised product **7** in moderate yield but as a complex mixture of stereoisomers. The formation of the double bond can be explained by oxidation of the resultant cyclised radical **6** to a cation followed by loss of a proton.[4]



Scheme 2

Reagents
(a) LDA, THF, -78°C then TMSCl, 87%
(b) Et_2Zn, CH_2I_2, Et_2O, 88%
(c) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, 50°C, 53%

Although the basic sequence was fairly efficient, the initial level of diastereoselection was disappointing. Since alkene formation was confusing the issue it was thought prudent to study a range of simpler cyclopropyl systems (e.g. **11**, Scheme 3) where complications arising from oxidation of the resulting cyclised primary radical would be unlikely. These were readily synthesised by conjugate addition of a number of Grignard reagents to the substituted acrylate esters **8** or **9**[5], in the presence of TMSCl, to give the corresponding ketene-acetals **10** in excellent yield. Cyclopropanation of these reactive[6] ketene-acetals with diethylzinc and diiodomethane gave the substituted cyclopropanone acetals **11** in good to excellent yield (Scheme 3, Table 1).



Scheme 3

Reagents
(a) BrMg⌒⌒ or RMgBr, CuI (10%), TMSCl, THF, HMPA, -78°C
(b) Et_2Zn, CH_2I_2, Et_2O
(c) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, 50°C

Ferric nitrate oxidation[7] of the cyclopropanone acetals **11** was carried out as before in anhydrous DMF using 1,4-cyclohexadiene as a hydrogen atom donor. In all cases oxidative cyclisation proceeded to give the cyclopentane esters **12a/b** in good yield (Table 1). The lower yield obtained for entry 4 was attributed to the volatility of the cyclised product. In general the diastereoselection obtained in these oxidative radical cyclisations correlated very well to the Beckwith model in Scheme 1. For example in entry 1 (R=Ph) the cyclised product **12a** was formed with essentially complete diastereoselection, with only trace amounts of other stereoisomers (**12b**) detectable by NMR. Proof of the relative stereochemistry in **12a** was obtained by nOe experiments on the reduced product **13** (Figure 1). Both the *n*-propyl (entry 3) and *iso*-propyl (entry 2) examples also gave good levels of selection. Although not quite as selective as the phenyl case these two results are consistent with a decrease in the size of the 2-substituent which would influence the preference for adopting a conformation where the substituent is equatorial. Not surprisingly when R=Me (entry 4) a poorer stereoselectivity was observed which is consistent with the results obtained with (±)-ethyl citronellate and clearly indicates the weaker stereochemical influence of the smaller methyl group.

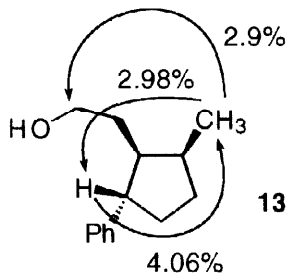
Table 1

Entry	R	10	11	12a/12b	Ratio[a] 12a:12b
1	Ph	92% (from **8**)	88%	75%	23:1
2	*iso*-C_3H_7	94% (from **9**)	70%	74%	8:1
3	*n*-C_3H_7	92% (from **9**)	76%	69%	6:1
4	Me	82% (from **8**)	66%	58%	2:1

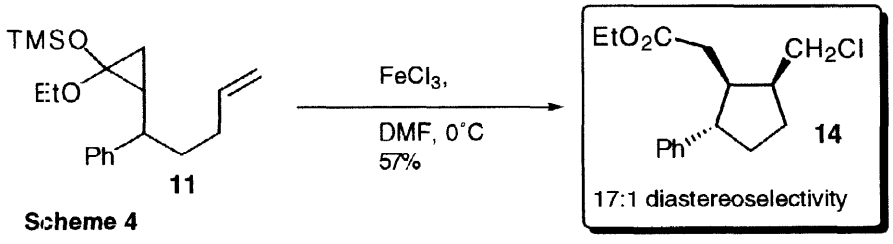
[a]Ratios determined by ^1H NMR

Figure 1

Selected nOe enhancements



Finally, equally good results were obtained in the oxidative cyclisations using ferric chloride as the iron source. For example treatment of the cyclopropanone acetal **11** (R=Ph) gave the trisubstituted chloromethyl cyclopentane ester **14** with a selectivity of 17:1. The incorporation of a chloromethyl group will be useful for the introduction of further functionality (Scheme 4).



Scheme 4

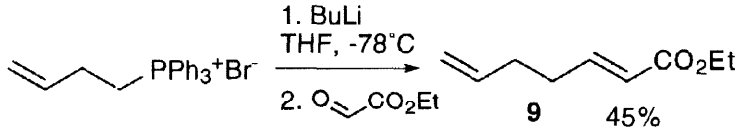
In summary, the Fe (III) mediated oxidative cyclisation of cyclopropanone acetals has been shown to be a highly effective method for the formation of functionalised cyclopentanes. The stereochemistry of these cyclisations are in good agreement with Beckwith's previous findings and give selectivities comparable to those obtained using classical tin hydride based methodologies.

Acknowledgements

We would like to thank the EPSRC for the provision of a research grant (GR/L23765) and Zeneca Pharmaceuticals for a CASE award (WB).

References and Notes

1. Booker-Milburn, K.I.; Thompson, D.F., *J. Chem. Soc. Perkin Trans. 1*, **1995**, 2315.
2. Booker-Milburn, K.I.; Cox, B.; Mansley , T.E., *Chem. Commun.*, **1996**, 2577.
3. (a) Beckwith, A.L.J.; Lawrence, T.; Serelis, A.K., *J. Chem. Soc.*, **1980**, 484; (b) Beckwith, A.L.J.; Easton, J.C.; Lawrence, T.; Serelis, A.K., *Aust. J. Chem.*, **1980**, 484; (c) Beckwith, A.L.J, *Tetrahedron*, **1981**, *37*, 3073; (d) RajanBabu, T.V., *Acc.Chem.Res.*, **1991**, *46*, 139.
4. For literature precedent of this type of oxidative termination see Snider, B.B.*Chem. Rev.*, **1996**, *96*, 339.
5. Ester **9** was prepared by the following Wittig sequence:



9 45%

6. In general the freshly distilled ketene-acetals **10** were used immediately in the next step since even short term storage results in extensive hydrolysis.
7. A solution of $Fe(NO_3)_3.9H_2O$ (2.18 g, 5.40 mmol) in DMF (10 ml) was stirred at room temperature over 4Å molecular sieves, under nitrogen, for 18 hours. To this burgundy solution at 50°C was added **11**(R=Ph, 0.5g, 1.73 mmol) and 1,4-cyclohexadiene (0.32 ml, 3.44 mmol) dropwise in dry DMF (10 ml). The solution was then stirred for a further 1 hour at 50°C before water (200 ml) was added. The resulting suspension was extracted with diethyl ether (3 x 200 ml). The organic layers were combined and washed with water (2 x 150ml), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to give a colourless oil. Purification by flash column chromatography (silica; 95% pet. ether, 5% ethyl acetate) gave a colourless oil (0.32g; 75%). ν_{max}/cm^{-1}(film) 1736 (C=O), 1602 (Ph). δH (270 MHz; C_6D_6) 0.90 (3H, d , J = 6 Hz, CH_3), 1.14 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.31-1.48 (1H, m), 1.61-1.82 (2H, m) 2.01-2.49 (5H, m), 2.72 (1H, m, CH), 3.91 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 7.14-7.27 (5H, m, Ph). δC (68.5 MHz; C_6D_6) 14.11 (CH_3), 16.03 (CH_3), 33.12 (CH_2), 33.48 (CH_2), 34.47 (CH_2), 35.25 (CH), 47.63 (CH), 49.52 (CH), 60.07 (CH_2), 126.13 (Ph), 127.64 (Ph), 128.37 (Ph), 173.33 (C=O). m/z 246 (M^+) Found: C 78.27%, H 8.76%. $C_{16}H_{22}O_2$ requires: C 78.05%, H 8.94%.