COMMUNICATION

ChemComm
www.rsc.org/chemcomm

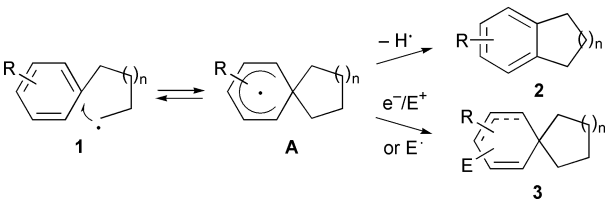
The first samarium(II)-mediated stereoselective spirocyclization onto an aromatic ring

Hiroaki Ohno, Shin-ichiro Maeda, Mitsuaki Okumura, Ryutaro Wakayama and Tetsuaki Tanaka*
Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

Received (in Cambridge, UK) 21st November 2001, Accepted 2nd January 2002
First published as an Advance Article on the web 21st January 2002

The first samarium(II)-mediated spirocyclisation onto an aromatic ring was achieved by the reaction of methyl 4-(4-oxoalkyl)benzoates with SmI_2 in the presence of *i*-PrOH and HMPA, yielding methyl 1-alkyl-1-hydroxyspiro-[4.5]dec-6-ene-8-carboxylates in moderate to high yields.

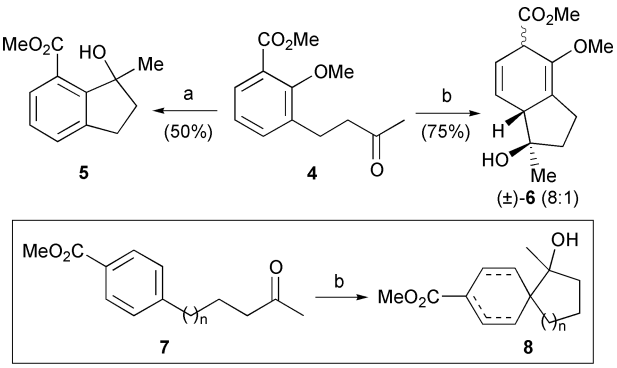
Radical cyclisation is one of the most useful methodologies for construction of spirocyclic quaternary carbon centres.[1] While the spirocyclisation by the reaction of tertiary radicals with alkene or alkyne multiple bonds is well documented,[2] radical spirocyclisation onto an aromatic nucleus (Scheme 1) is relatively limited. This is presumably due to both the instability of spirocyclohexadienyl radical intermediate **A** and the reversible nature of the radical addition.[3,4] The intermediate **A** can be easily converted into an alkyl radical (**1** or another)[3] or a more stable condensed ring **2**.[4]



Scheme 1

When the unstable radical species **A** can be oxidised or reduced efficiently, spirocyclic compounds such as **3** could be obtained from the aromatic ring with a loss of aromaticity. Although some examples of the radical spirocyclisation onto an aromatic ring have been reported,[5] samarium(II)-mediated formation[6] of spirocycles by this process is unknown as far as we are aware.[7]

Recently, we have reported that treatment of **4** with SmI_2 yields *ipso*-substituted product **5** (Scheme 2).[8] The detailed investigation of this reaction revealed that addition of HMPA to the reaction mixture dramatically changes the cyclisation mode: thus, treatment of **4** with SmI_2 in the presence of HMPA[9] and *i*-PrOH yielded a condensed ring **6** bearing a cyclohexadienyl moiety as a diastereomeric mixture (8:1).[10] Considering that the ketyl radical attacks at the *para*-position of the ester group of **4**, we expected that the radical spirocyclisation onto an aromatic ring could be possible when using benzoates such as **7** bearing an oxoalkyl group at the *para*-position to the ester group. We report herein a samarium(II)-mediated stereoselective spirocyclisation *via* intramolecular radical addition onto electron-poor aromatic rings. This is a reaction of considerable interest in that the ketyl radical can attack at a more hindered aryl carbon.[11]



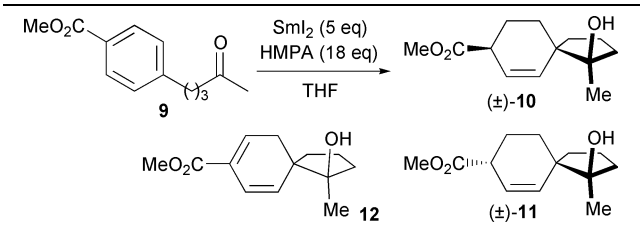
Scheme 2 *Reaction conditions*: (a) SmI_2 (3.5 equiv.), THF; (b) SmI_2 (5 equiv.), HMPA (18 equiv.), *i*-PrOH (2 equiv.), THF, 0 °C.

First, we prepared benzoate **9** bearing a 4-oxopentyl group on the *para*-position, and investigated the samarium(II) iodide-promoted cyclisation. Selected results are summarised in Table 1. As we expected, treatment of **9** with THF solution of SmI_2 in the presence of HMPA (18 equiv.) and *i*-PrOH (2 equiv.) gave spirocyclic compounds **10** and **11** in 50% yield (**10**:**11** = 1.7:1, entry 1). Increased loading of *i*-PrOH (entry 2) or HMPA was less effective. Although some other proton source such as H_2O or 2,6-di-*tert*-butyl-4-methylphenol (BHT)[12] was employed (entries 3 and 4), a considerable amount of the starting material was recovered or dienylspirocyclic compound **12** was obtained. However, lowering the reaction temperature to 0 °C increased the yield of **10** and **11** (93% yield, entry 6). In all cases, the relative stereochemistry of the spirocyclic quaternary centre and the neighbouring quaternary carbon was completely controlled.[13]

As shown in Scheme 3, ethyl ketone **13** and aldehyde **14** were used comparably for the present spirocyclisation. In both cases, the desired spirocycles **15**–**18** were isolated in moderate yields (51 and 57%, respectively). When a spiro[5.5]undecene precursor **19** was subjected to the samarium(II)-mediated cyclisation, the expected spiro compounds **20** and **21** were obtained (**20**:**21** = 1.6:1), although other unidentified products were also produced.

Finally, the reactions of *ortho*- and *meta*-substituted benzoates **22** and **23** were investigated. As shown in Scheme 4, *ortho*-substituted benzoate **22** gave the desired spiro compounds **24**

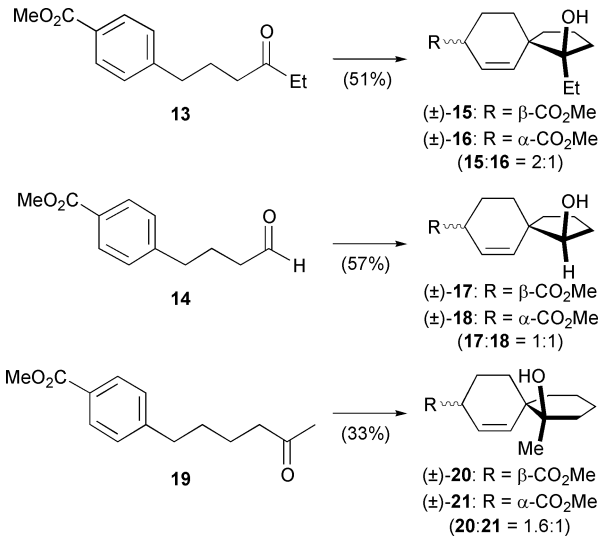
Table 1 Spirocyclisation of **9**[a]



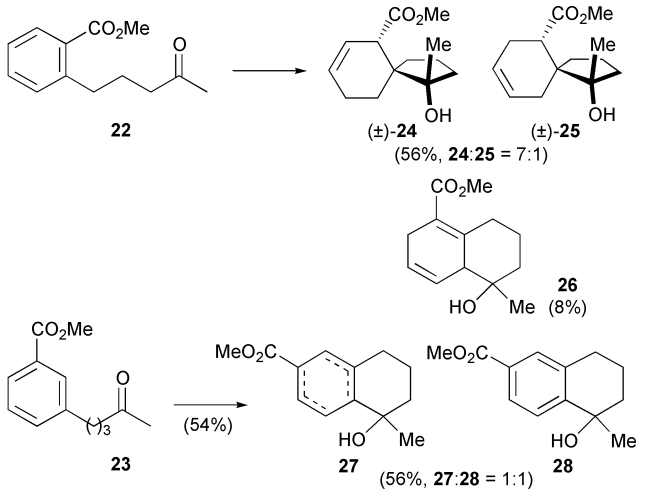
Entry	ROH (equiv.)	Temp.	**10** + **11**	Ratio[b] (**10**:**11**)	**12**
1	*i*-PrOH (2)	rt	50%	1.7:1	0%
2	*i*-PrOH (10)	rt	55%	2:1	0%
3	H_2O (2)	rt	9%	2.5:1	0%
4	BHT[c] (2)	rt	12%	2:1	17%
5	none	rt	10%	2:1	18%
6	*i*-PrOH (2)	0 °C	93%	1:1.3	0%
7	*i*-PrOH (2)	−78 °C	84%	1.7:1	0%

[a] All the reactions were carried out in THF using 5 equivalents of SmI_2. [b] BHT = 2,6-di-*tert*-butyl-4-methylphenol. [c] Ratios were determined by ^1H NMR.

DOI: 10.1039/b110633c



Scheme 3 *Reaction conditions*: SmI_2 (5 equiv.), HMPA (18 equiv.), *i*-PrOH (2 equiv.), THF, rt.

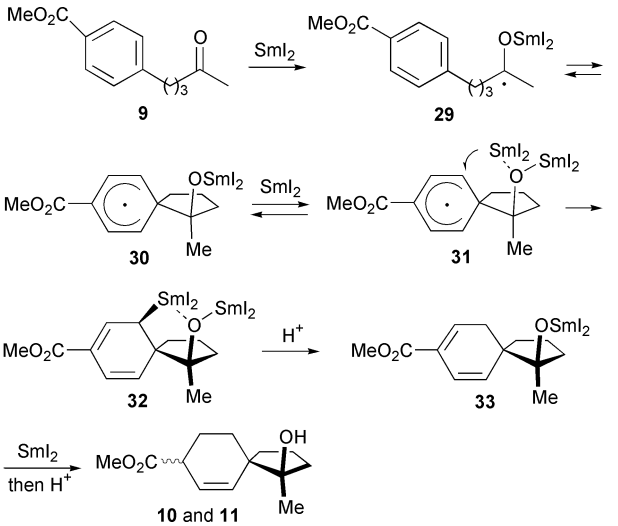


Scheme 4 *Reaction conditions*: SmI_2 (5 equiv.), HMPA (18 equiv.), *i*-PrOH (2 equiv.), THF, 0 °C.

and **25** in 56% yield (**24**:**25** = 7:1). In this case, a small amount of a condensed ring **26** was obtained (8% yield) along with other products. The undesired **26** would be produced by the rearrangement of the cyclohexadienyl radical intermediate **A** (Scheme 1),[4] followed by single electron transfer by SmI_2. As we expected, cyclisation of *meta*-substituted benzoate **23** afforded no spiro compound, yielding an unstable condensed cyclohexadiene **27** and an aromatised compound **28** (54%, **27**:**28** = 1:1). The diene **27** was gradually converted into **28** during purification. From these observations, the ketyl radicals can attack the substituted benzene ring at the *para*- or *ortho*-position to the ester group.

As shown in Scheme 5, this spirocyclisation will proceed *via* the ketyl radical intermediate **29**. Cyclisation of **29** would occur onto the more reactive carbon (*para*- or *ortho*-position to the ester group) to give the unstable cyclohexadienyl radical intermediate **30**. Another molecule of SmI_2 reduces **30** from the side of the oxygen atom as depicted in **31**, and cyclohexadienyl anion **32**[14] will be produced stereoselectively. Finally, alcoholysis of **32** followed by 1,4-reduction of the resulting enoate **33**[15] by SmI_2 gives a diastereomixture of **10** and **11**.

In conclusion, we have demonstrated the first samarium(II)-mediated spirocyclisation onto an aromatic ring. This reaction can serve as a stereoselective synthetic route to highly congested spirocyclic compounds. Further studies including the reaction of substrates bearing other electron-withdrawing groups are now under way in this laboratory.



Scheme 5

Notes and references

1 For a recent review, M. Sannigrahi, *Tetrahedron*, 1999, **55**, 9007.

2 D. S. Middleton and J. S. Simpkins, *Tetrahedron Lett*., 1988, **29**, 1315; M. Ishizaki, K. Ozaki, A. Kanematsu, T. Isoda and O. Hoshino, *J. Org. Chem*., 1993, **58**, 3877; C.-K. Sha and W.-Y. Ho, *Chem. Commun*., 1998, 2709; A. Srikrishna, S. Nagaraju, S. Venkateswarlu, U. S. Hiremath, T. J. Reddy and P. Venugopalan, *J. Chem. Soc., Perkin Trans 1*, 1999, 2069.

3 H. Ishibashi, N. Nakamura, K. Ito, S. Kitayama and M. Ikeda, *Heterocycles*, 1990, **31**, 1781; A. Citterio, R. Sebastiano, A. Maronati, R. Santi and F. Bergamini, *J. Chem. Soc., Chem. Commum*., 1994, 1517.

4 N. S. Narasimhan and I. S. Aidhen, *Tetrahedron Lett*., 1988, **29**, 2987; P. C. Montevecchi and M. L. Navacchia, *J. Org. Chem*., 1998, **63**, 537.

5 D. H. Hey, G. H. Jones and M. J. Perkins, *J. Chem. Soc. (C)*, 1971, 116; C.-C. Yang, H.-T. Chang and J.-M. Fang, *J. Org. Chem*., 1993, **58**, 3100; J. Boivin, M. Yousfi and S. Z. Zard, *Tetrahedron Lett*., 1997, **38**, 5985; C. Escolano and K. Jones, *Tetrahedron Lett*., 2000, **41**, 8951.

6 For recent reviews on samarium iodide chemistry: P. G. Steel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2727; G. A. Molander and C. R. Harris, *Tetrahedron*, 1998, **54**, 3321.

7 For samarium(II)-mediated spirocyclisation by the addition of the ketyl radicals onto alkenes, see: K. Shibuya, H. Nagaoka and Y. Yamada, *J. Chem. Soc., Chem. Commum*., 1991, 1545; C. A. Merlic and J. C. Walsh, *J. Org. Chem*., 2001, **66**, 2265; M. Sono, Y. Nakashiba, K. Nakashima, S. Takaoka and M. Tori, *Heterocycles*, 2001, **54**, 101.

8 T. Tanaka, R. Wakayama, S. Maeda, H. Mikamiyama, N. Maezaki and H. Ohno, *Chem. Commum*., 2000, 1287.

9 J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett*., 1987, 1485.

10 For related reactions: C. U. Dinesh and H.-U. Reissig, *Angew. Chem., Int. Ed*., 1999, **38**, 789; M. Berndt and H.-U. Reissig, *Synlett*, 2001, 1290.

11 For samarium(II)-mediated cyclisation onto an aromatic ring, see: H.-G. Schmalz, S. Siegel and J. W. Bats, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 2383; C.-W. Kuo and J.-M. Fang, *Synth. Commun*., 2001, **31**, 877. See also, refs 8 and 10. For a related reaction, see: S. M. Yang, S. K. Nandy, A. R. Selvakumar and J.-M. Fang, *Org. Lett*., 2000, **2**, 3719.

12 BHT is known as a selective protonating reagent for metal enolates: Z. Hou, T. Yoshimura and Y. Wakatsuki, *J. Am. Chem. Soc*., 1994, **116**, 11169; C. Fehr and J. Galindo, *Angew. Chem., Int. Ed*., 1994, **33**, 1888.

13 Stereochemistries of spirocycles were determined by epoxydation or base-mediated isomerisation of the double bonds.

14 For related intermediates, see: S.-C. Lin, F.-D. Yang, J.-S. Shiue, S.-M. Yang and J.-M. Fang, *J. Org. Chem*., 1998, **63**, 2909; S.-M. Yang and J. M. Fang, *J. Org. Chem*., 1999, **64**, 394.

15 Inanaga and co-workers reported that sterically crowded α,β-unsaturated enoates undergo reduction of the double bond by SmI_2–HMPA, see: J. Inanaga, Y. Honda, T. Tabuchi, K. Ohtsubo, M. Yamaguchi and T. Hanamoto, *Tetrahedron Lett*., 1991, **32**, 6557.