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Enantioselective Synthesis of Spiro[4.4]non- and Spiro[4.5]dec-2-ene-1,6-diones

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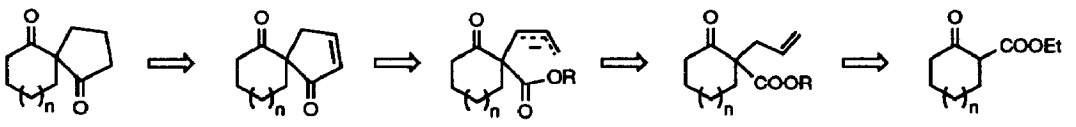
Abstract: *Spiro[4.4]non- and spiro[4.5]dec-2-ene-1,6-diones [2; n = 0 and 1] were prepared in moderate to high enantiomeric purities via asymmetric allylation of enamines 6 and ketal derivatives 7 and 8 formed from keto-esters 5, followed by a carbanionic cyclization process.*

Spiro[4.5]decane-1,6-dione, **1**, has been used as the building block for the synthesis of spirocyclic natural products, *e.g.* perhydrohistrionicotoxin,[1] hence efforts have been geared towards the synthesis of molecules such as **1**, both in racemic and enantiomeric forms.[2] Since **1** can be directly obtained from **2** which, in turn, could in principle be synthesized *via* a direct three carbon annelation route reported earlier,[3] it was anticipated that a route involving asymmetric allylation of the commercially available keto-ester **5**, employing a cheap and readily available chiral template, would offer a convenient and economical entry to optically active **2**, thence **1**.

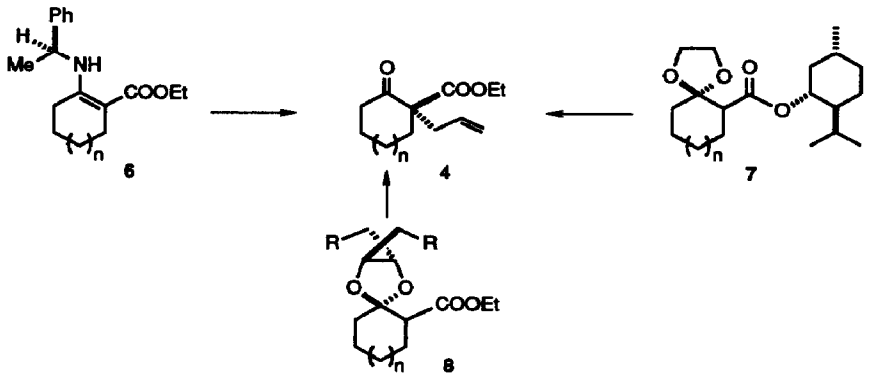
Scheme 1

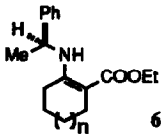
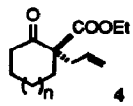
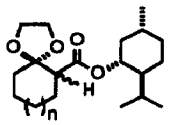
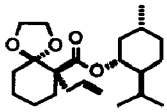
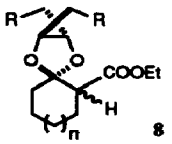
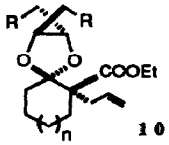


Various approaches were studied for the asymmetric allylation of keto-ester **5**: these include the use of optically active enamine **6**,[4] menthyl ester **7**[5] and ketal **8**,[6] derived from the reactions of **5** with (*S*)-(-)-α-methylbenzylamine, (1*R*,2*S*,5*R*)-(-)-menthol, and derivatives of (2*R*,3*R*)-(+)-tartaric acid respectively (Scheme 2). The results are summarized in the TABLE.

All allylation reaction steps shown were conducted at –78° since it was found that the products obtained from reactions at higher reaction temperatures, *e.g.* at –30° or 0°, showed inferior optical yields (although chemical yields were comparable), and the results from reactions conducted at higher temperatures are deliberately omitted from the TABLE for clarity. Secondly, all the results shown in the TABLE were confirmed

Scheme 2



entry	starting material	conditions	product	% yield[a]	% ee[b]
		i) LDA (2.2 eq) / THF / –78° then  (1 eq) / –78° / 5h ii) 10% AcOH / THF / Δ			
1	n = 0		n = 0	71	64
2	n = 1		n = 1	76	35
		i) LDA (3.0 eq) / solvent / –78° then  (1 eq) / –78° / 5h ii) TsOH(cat.) / benzene / Δ / 2h			
		solvent			
3	n = 1	THF only		73	46
4		THF / HMPA = 10:1		96	34
5		THF / TMEDA = 10:1		84	25
		i) LDA (3.0 eq) / solvent / –78° then  (1 eq) / –78° / 5h ii) TsOH(cat.) / benzene / Δ / 3h			
		solvent			
6	n = 0; R = Ph	THF ONLY	n = 0; R = Ph	73	0
7	n = 0; R = OMe		n = 0; R = OMe	78	46
8	n = 0; R = OCH_2Ph		n = 0; R = OCH_2Ph	71	50
9	n = 1; R = Ph		n = 1; R = Ph	75	0
10	n = 1; R = OMe		n = 1; R = OMe	68	37
11	n = 1; R = OCH_2Ph		n = 1; R = OCH_2Ph	74	79
		solvent			
12	n = 0; R = OCH_2Ph	THF / HMPA = 10:1	n = 0; R = OCH_2Ph	53	55
13	n = 0; R = OCH_2Ph	THF / TMEDA = 10:1	n = 0; R = OCH_2Ph	68	69
14	n = 1; R = OCH_2Ph	THF / HMPA = 10:1	n = 1; R = OCH_2Ph	93	76
15	n = 1; R = OCH_2Ph	THF / TMEDA = 10:1	n = 1; R = OCH_2Ph	95	88

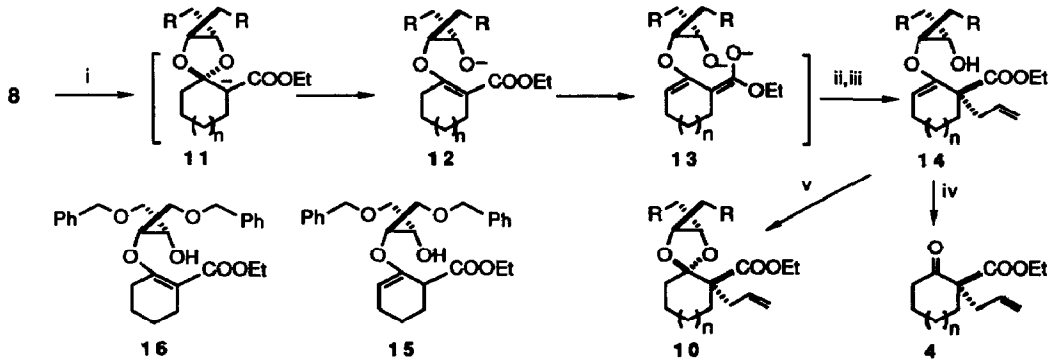
a) isolated yield *b)* see ref. 8

by the use of antipodal chiral templates to obtain the corresponding products with opposite configurations.

Allylation of lithium salts generated from enamines **6** followed by hydrolysis of the crude products gave allyl keto-esters **4** in moderate yields with the five-membered ring analogue (**4**, n = 0) showing better chiral induction (entries 1 and 2 in TABLE). Moderate asymmetric induction was also observed in the case of the menthyl ester **7**; however it was noticed that solvent played an important role in the reaction.[4c] Addition of a chelating agent, *e.g.* HMPA or TMEDA, resulted in better chemical yields but with lower enantiomeric purities (entries 3 - 5). Allylation of the ketal ester **8** is very interesting, as chiral induction varies from zero (R = Ph, entries 6 and 9), moderate (R = OMe, entries 7 and 10), to quite respectable when R = OCH_2Ph (entries 8 and 11). Further study on the allylation of the latter (**8**, R = OCH_2Ph) revealed that unlike the case of menthyl ester **7** discussed earlier the enantiomeric purity of product **10** could be improved by the use of metal chelater. Thus, THF/ HMPA (10:1) solvent system improved the ee values of products **10**, R = OCH_2Ph, n = 0 and 1, to 55% and 76% respectively (entries 12 and 14) while best results (ee 69% and 88%) were obtained when THF/ TMEDA was employed (entries 13 and 15).

It should be noticed that excess LDA (*i.e.* 3 equivalents) was employed in the allylation reaction of starting materials **7** and **8**. This was due to the fact that the ketal moiety of the first-formed enolate, *e.g.* **11**, rapidly ring opened to give alkoxide **12** followed by the generation of ester dienolate **13**[7] which was allylated upon the addition of allyl bromide. In a control experiment employing the ketal ester **8** (n = 1, R = OCH_2Ph) as starting material the corresponding alcohol **14** was obtained in 75% isolated yield together with trace amounts of the non-allylated products **15** and **16**. As summarized in Scheme 3 the ring-opened alcohol **14** readily provided either product **10** or **4** upon treatment with a catalytic amount of *p*-toluenesulphonic acid in boiling benzene or heating in methanol in the presence of aqueous hydrochloric acid. Similar results were obtained in the case of menthyl ester **7**.

Scheme 3

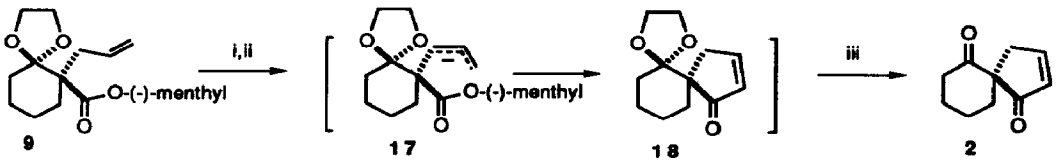


i) LDA (3.0 eq), THF, -78°; ii) CH_2=CH-CH_2Br, (1.0 eq), -78°, 5h; iii) H_3O^+

iv) (2M) HCl-MeOH, reflux 8 hr; v) *p*-TsOH, benzene, reflux 3 h

Cyclization of **9** *via* the allyl carbanionic method[3] was straightforward, giving the cyclopentenone **18** which, without purification, was further converted to the desired product **2** with preservation of chirality[8] (Scheme 4).

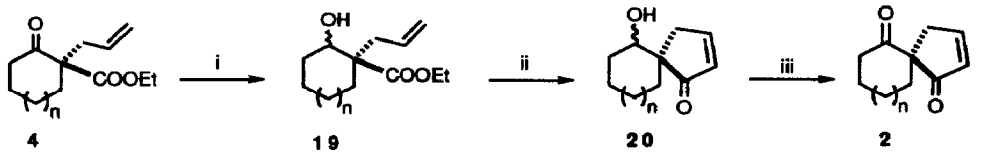
Scheme 4



i) LDA (2.2eq), THF:TMEDA (4:1), room temp.; ii) H_3O^+; iii) *p*-TsOH,acetone, H_2O, reflux 2 h

However, annelation reactions of **10** (n = 0,1 ; R = Ph, OCH_2Ph) gave only low yields of the expected products. This was probably due to the presence of the benzylic moieties in the molecules which interfered with the allyl anion formation step (*e.g.* **17**). The problem was easily overcome by the conversion of **10** to the keto-ester **4** followed by borohydride reduction of the keto group, cyclization, and finally, PCC oxidation of the spiro keto-alcohol **20** to obtain the target molecule **2** (n = 0, 69 % ee ; n = 1, 88 % ee) as shown in Scheme 5. This latter reaction sequence (Scheme 5), though diverted, is highly efficient and promising with regard to extending the scope of the three-carbon annelation method in organic synthesis.

Scheme 5



i) $NaBH_4$, EtOH; ii) LDA, THF:TMEDA (4:1),room temp.; iii) PCC, CH_2Cl_2

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