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Enantioselective Synthesis of 2,2-Dialkyltetrahydropyran-3-ones via the Asymmetric Michael Addition Reaction using Chiral Imines

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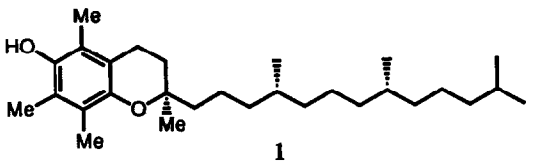
Key words: *Chiral imine ; asymmetric Michael addition reaction; chiral 2,2- dialkyltetrahydropyran-3-ones; circular dichroism.*

Abstract: *Addition of chiral imine 8 derived from 2-methyltetrahydropyran-3- one 7 and R-(+) - 1- phenylethylamine, to methyl acrylate led to adduct (S)-9 with a good yield and an excellent stereoselectivity.*

2,2-Dialkylated hydropyrans are key structural features frequently encountered in biologically active molecules of natural or synthetic origin. Thus, for example, α-tocopherol (vitamine E) **1** is an essential nutritional factor in mammals[1] and pemedolac **2**, a highly potent analgesic, antiinflammatory agent[2].



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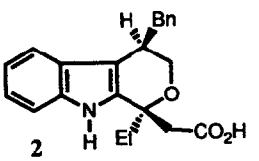
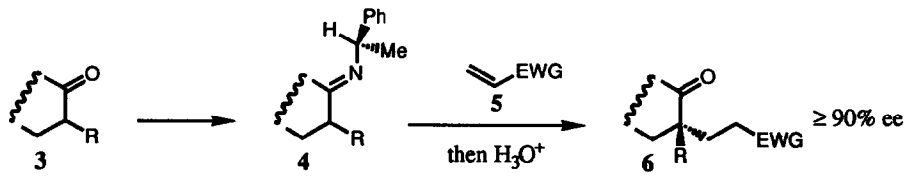


2

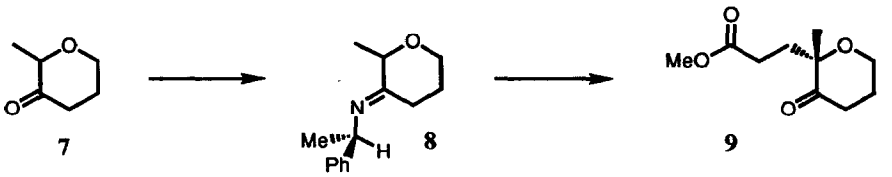
The aforementioned heterocyclic moieties exhibit two geminal appendages on a stereogenic center. In this regard, they could be enantioselectively elaborated by using the asymmetric Michael addition process we have reported, typified by equation [**3**→**6**][3] .Thus chiral imines **4**, derived from *racemic* 2-alkylcyclanones **3** and optically active 1-phenylethylamine add to electrophilic alkenes **5** leading, after hydrolytic work-up, to 2,2-dialkylcyclanones **6** with a high degree of regio- and stereoselectivity.



3 **4** **6**

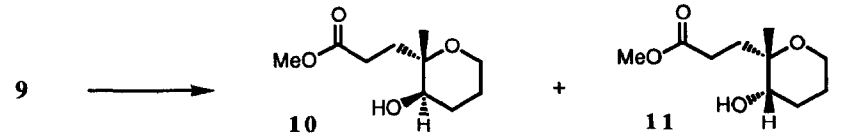
Very interestingly, this asymmetric process tolerates the presence of an oxygen atom at the α-position relative to the carbonyl group of the starting cyclanone, *either in the exocyclic*[4] *or endocyclic*[5] *situation.* In this respect, this reaction has been applied to the furanone series (preparation of optically active 2,2-dialkyltetrahydrofuran-3-ones)[5]. In the present paper we show that this methodology could be extended with success to the six-membered analogues, adduct **9** being obtained with a good yield and an excellent selectivity.

Imine **8** has been prepared from 2-methyl-tetrahydropyran-3-one **7**[6] and *R*-(+)-1-phenylethylamine ($[\alpha]_D$ +39.1, neat, 96% ee)[7].This crude imine was added to methyl acrylate (2 eq, neat, 48 h, 45 °C) leading, after hydrolytic treatment (AcOH/ H_2O/ THF), to adduct *S*-(+)-**9** (70% yield from **7**, 94% ee).

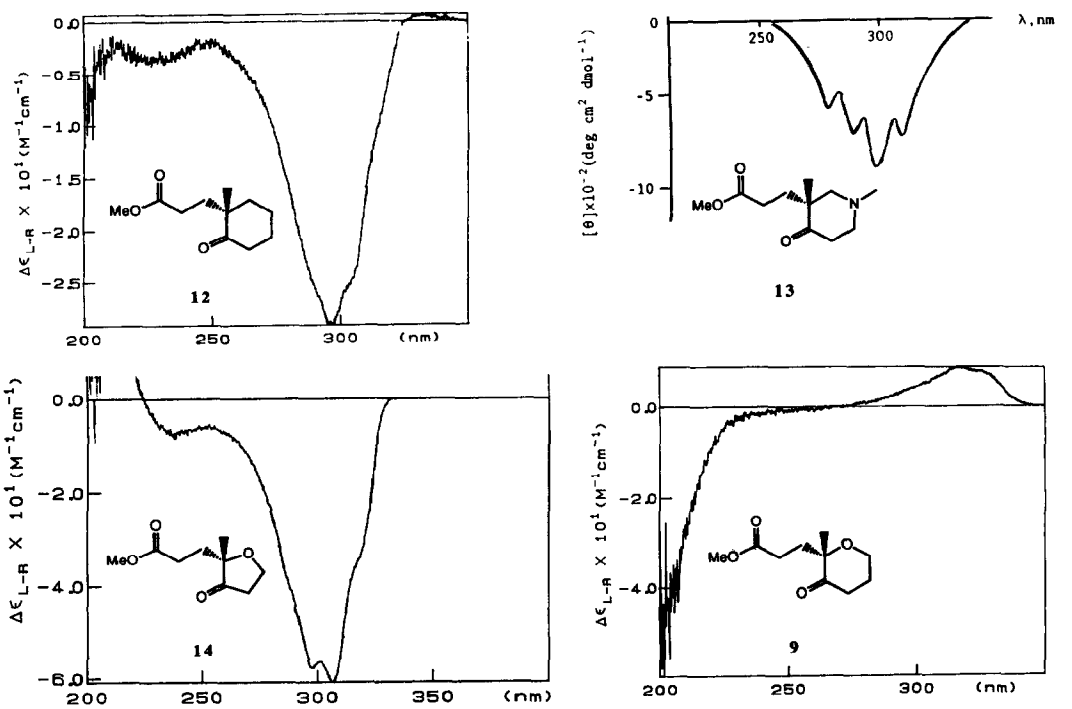


Determination of ee and absolute configuration in adduct 9

Since direct determination of the ee in adduct **9** by NMR techniques proved to be fruitless, this compound was reduced ($NaBH_4$) into a 1.2:1 mixture of epimeric alcohols **10** and **11**, easily separated by flash chromatography. The ee (94%) of the major isomer **10** was then established by ^1H NMR, using $Eu(hfc)_3$ as shift reagent. Based upon the ee of the chiral auxiliary amine being 96%, *the efficacy of the "chirality transfer" in the present asymmetric process is 98%.*

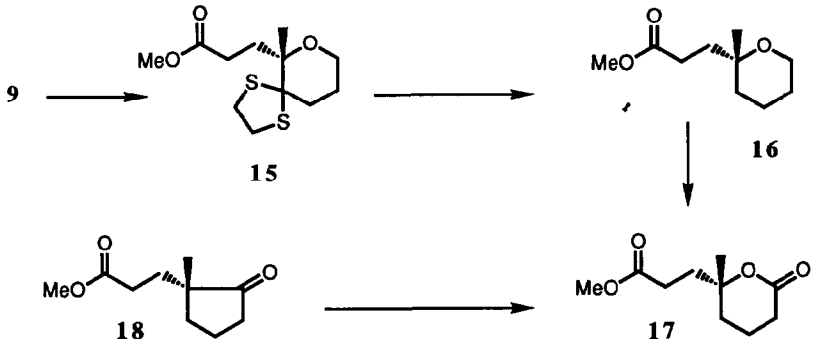


Determination of absolute configuration of adduct **9** (assumed to be *S*, as depicted, considering the proposed transition-state model for these Michael additions[3]) was then attempted, by comparing its circular dichroism (CD) spectrum with those of the closely related molecules **12**[10], **13**[11] and **14**[5], of known configuration. However while compounds **12**, **13** and **14** show similar *negative* Cotton effects centered in the 300 nm region (corresponding to the $n \rightarrow \pi^*$ transition of the carbonyl chromophore), molecule **9** exhibits a *positive* absorption at *ca* 320 nm.

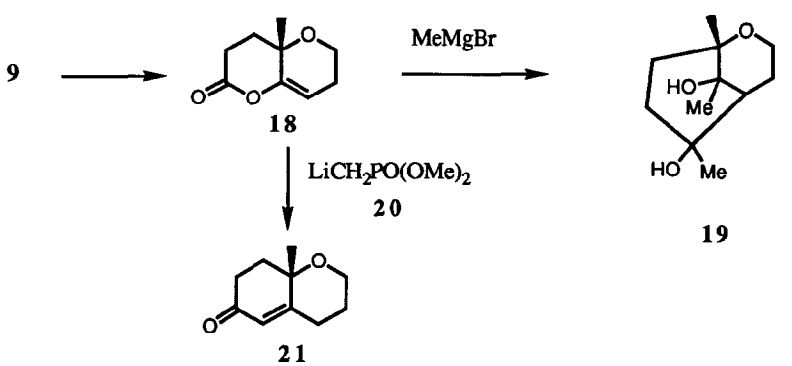


Such a methodology, based on the comparison of CD spectra, proved therefore to be non-conclusive in the present case.

In view of the "abnormal" CD spectrum of **9**, we next decided to assign its absolute configuration by chemical correlation with the known ketoester (*R*)-**18**[10]. For this purpose, compound **9** was first converted into thioketal **15** (1,2-ethanedithiol, AcOH, $TiCl_4$, 20°C, 12 h). Desulfurization of **15** (Raney nickel, 3 h in refluxing MeOH) gave (*R*)-**16**[12] which, upon oxidation ($RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O)[13], furnished lactone (*R*)-**17**[14]. The latter derivative was found to be identical in all respects with an authentic sample prepared unambiguously through the Baeyer-Villiger oxidation of known (*R*)-**18**[10] (3-chloroperbenzoic acid, 24 h in refluxing CH_2Cl_2, 60% yield).



In order to synthesize bicyclic enone **21**, addition of methylvinylketone to imine **8** was also examined. However, regardless of the operating conditions, this reaction has invariably furnished a complex mixture of mono- and polyalkylated adducts, a severe drawback we have previously pointed out in the furanone serie[5]. To overcome this difficulty, ketoester **9** was first transformed into enol lactone **18** (*i*: 2N NaOH in MeOH, 2 h, 20°C; *ii*: AcONa, 4 h in refluxing Ac_2O) and the conversion of this derivative into **21**, by using the Belleau-Fujimoto procedure[15] (addition of MeMgBr), was next attempted. Unfortunately, even under carefully controlled operating conditions, this addition was thwarted by a competitive side-reaction, leading to important amounts of bridged compound **19**[16] (the formation of the latter product becoming nearly quantitative when 2 eq of Grignard reagent is used). Synthesis of (*S*)-**21**[17] was finally efficiently achieved by adding the lithio derivative **20**, developed by Corey[18], to **18** (4 h at -20°C).



Conversion of adduct **9** into fused octahydro pyrano-pyran subunits related to polyether toxins of marine origin is presented in the forthcoming paper.

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6 Gore, J. ; Guigues, F. *Bull. Soc. Chim. Fr.*, **1970**, 3521.

7 Imine **8** was prepared by stirring a cyclohexane solution of an equimolar mixture of ketone **3** and chiral amine (12 h, 20°C, 1 mmole of reagents in 2 ml of cyclohexane in the presence of 0.4 g of catalyst[8], itself prepared by calcinating before use with a free flame at 0.1 Torr a mixture of 56 g of powdered 5 Å molecular sieves, 10 g of basic alumina type E and 5 g of silica gel for flash chromatography).

8 Roelofsen, D. P. ; van Bekkum, H. *Rec. Trav. Chim.*, **1972**, *91*, 605.

9 **9**: oil; bp 100°C (0.05 Torr); $[\alpha]_D^{20}$ -4.0 (neat); MS (EI, 70 eV) m/e: 200 ($M^{+\cdot}$,2) 172 (17) 169 (21) 131 (21) 115 (25) 113 (15) 99 (100); IR (neat) 1755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (s, 3H) 1.8 - 2.4 (m, 5H) 2.52 (t, J=6.8 Hz, 2H) 3.66 (s, 3H) 3.86 (t, J=5.8 Hz, 2H); ^{13}C NMR(20 MHz, $CDCl_3$) δ 21.4 (CH_3) 25.7 (CH_2) 28.4 (CH_2) 31.8 (CH_2) 35.6 (CH_2) 51.6 (CH_3) 60.3 (CH_2) 82.3 (C) 173.8 (C) 211.5 (C) .

10 Pfau, M. ; Revial, G. ; Guingant, A. ; d'Angelo, J. *J. Am. Chem. Soc.*, **1985**, *107*, 273.

11 Gaidarova, E.L. ; Grishina, G.V. *Synlett*, **1992**, 89.

12 **16** : oil; bp 50°C (0.01 Torr); $[\alpha]_D^{20}$ +8.3 (c=2, EtOH); MS (EI, 70 eV) m/e 186($M^{+\cdot}$, 1) 171(6) 155(6) 99(100); IR (neat) 1735 cm^{-1} ^1H NMR (200 MHz, $CDCl_3$) δ 1.14(s, 3H)1.43-1.72(m,7H) 2.09(m, 1H) 2.38(m, 2H) 3.58-3.65(m, 2H) 3.67(s,3H),^{13}C NMR(50 MHz, $CDCl_3$) δ 19.2 23.3 25.7 28.2 33.7 35.2 51.4 61.4 71.9 174.6.

13 Carlsen, Per H. J. ; Katzuki, T. ; Martin, V. S. ; Sharpless, K. B. *J. Org. Chem.* , **1981**, *46*, 3936.

14 **17**: oil; $[\alpha]_D^{20}$ +12.0 (c=1, EtOH); IR (neat) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H) 1.7-1.85 (m, 2H) 1.85-2.0 (m, 3H) 2.0-2.15 (m, 1H) 2.35-2.6 (m, 4H) 3.30 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 17.0 (CH_2) 26.4 (CH_3) 28.9 (CH_2) 29.8 (CH_2) 32.8 (CH_2) 36.9 (CH_2) 52.3 (CH_3) 83.6 (C) 171.3 (C) 174.1 (C).

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16 **19**: white crystals; mp 148°C; $[\alpha]_D^{20}$ +35.2 (c=2.8, EtOH); MS (EI, 70 eV) m/e 200($M^{+\cdot}$, 5)182 (5) 167 (7) 154 (10) 125 (38) 111 (100); IR ($CDCl_3$) 3600-3400 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 3H) 1.29 (s, 3H) 1.38 (s, 3H) 1.6-2.3 (m, 6H) 3.66 (dd, J=8.5 12 Hz, 1H) 4.06 (dt, J=8.5 4.7 Hz, 1H) 4.9 (s, 2H); ^{13}C NMR(50 MHz, $CDCl_3$) δ 22.6 23.9 26.0 29.8 30.4 37.0 47.9 60.7 73.7 74.8 75.0.

17 **21**: oil; $[\alpha]_D^{20}$ +204 (c=4, EtOH); IR (neat) 1670 1625cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H) 1.75 (m, 2H) 1.95 (m, 1H) 2.08 (dt, J=13.1 5.9 Hz, 1H) 2.2-2.6 (m, 4H) 3.7-3.9 (m, 2H) 6.54 s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7 (CH_3) 27.0 (CH_2) 29.2 (CH_2) 35.0 (CH_2) 36.8 (CH_2) 61.1 (CH_2) 72.9 (C) 124.2(CH) 164.2 (C) 198.2 (C).

18 (a) Corey, E. J; ; Kwiatkowski, G.T. *J. Am. Chem. Soc.*, **1966**, *88*, 5653. (b) Henrick, C. A. ; Böhme, E. ; Edwards, J. A. ; Fried, J. H. *Ibid.*, **1968**, *90*, 5926.