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ENANTIOSELECTIVE SYNTHESIS OF OXA-SPIRO COMPOUNDS

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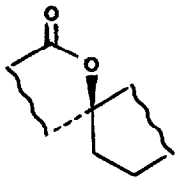
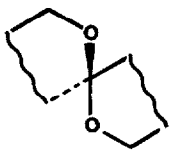
Abstract *: Optically active compound **10b**, efficiently prepared from imine **8b**, was transformed into oxa-spiro derivatives **15** and **16**.*

The spirolactone moiety **1**, and related spiroketal unit **2**, are key structural features of many biologically active compounds. Thus, for example, the important diuretic drug spironolactone [1] contains the spirolactone system, while the spiroketal structure is found in certain Insect pheromones (*e.g.* olive-fly [2] and common wasp [3] pheromones), as well as in the mycotoxins talaromycins [4], antihelmintics avermectins and milbemycins [5], and in most of the ionophore antibiotics.

To our knowledge, no simple, direct route for the enantioselective elaboration of the spirolactone moiety has been proposed to date. In this paper we report a short, efficient asymmetric synthesis of the cyclohexanone derivatives **9**, **10**, and the easy conversion of one of these (**10b**) into target oxa-spiro compounds **15** and **16**.



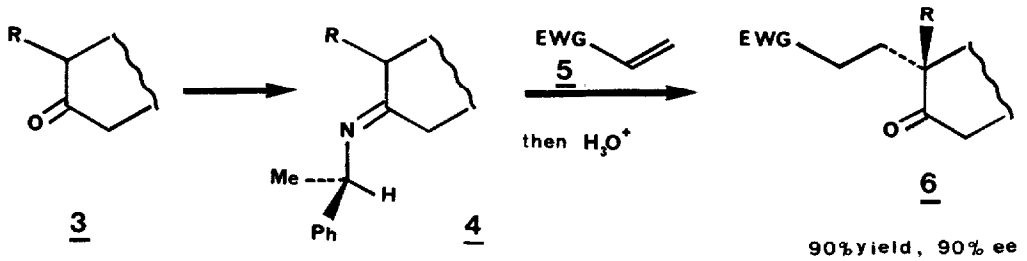
1



2

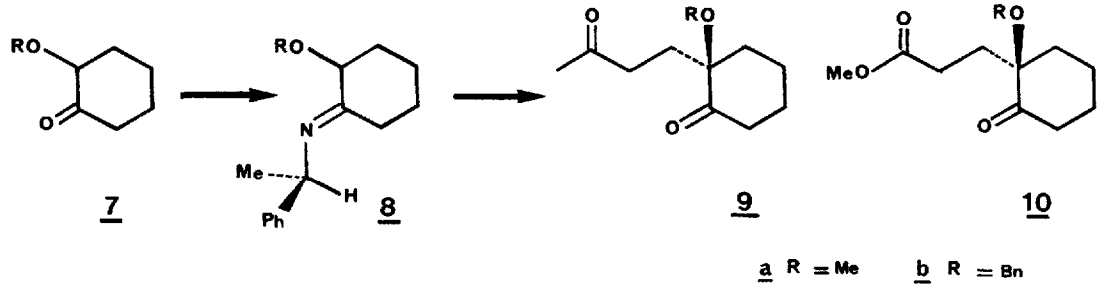
The present synthetic design is, in fact, closely connected to an exceptionally potent asymmetric Michael process we have recently described, involving the *"deracemizing alkylation"* of α-substituted cyclanones **3**, through the conjugate addition of their chiral imine derivatives **4** to electrophilic alkenes **5** [6]. Remarkably, this alkylation generally takes place almost exclusively at the *more* substituted α position of the imine, leading to optically active α-disubstituted cyclanones **6**.

Such a methodology seems *a priori* well-suited to the enantioselective construction of compounds **9**, **10**, provided that the presence of the alkoxy substituent in the required starting cyclohexanones **7** does not notably alter the two remarkable features of this process, namely the high degree of regiochemical and stereochemical control. This is actually the case, as shown in the following experiments.



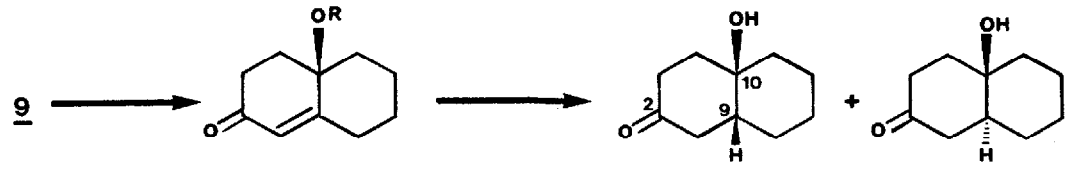
Thus, addition of crude imines **8** (prepared from alkoxy-2 cyclohexanones **7** [7] and (*R*)-(+)-1-phenylethylamine, cyclohexane, 20 °C, 24 h, in the presence of an activated catalyst [8]) to methylvinylketone (THF, 20 °C, 3 days, followed by treatment with 20 % aqueous AcOH), gave (*R*) adducts **9** [9] with a 75 % overall yield. Similarly, addition of these imines to methyl acrylate (neat, 40 °C, 4 days), led to (*R*) adducts **10** [10] (80 % yield). It should be noted that, in the former reaction, a significant amount (*c.a.* 10 %) of regioisomers of compounds **9** –the result of the alkylation at the less substituted α position of imines **8**– could be detected (these having easily been removed by flash chromatography), while the alkylation reaction using methyl acrylate was almost completely regioselective.

Inspection of the ^1H NMR spectrum of compound **10a** revealed, in the presence of a chiral shift reagent, splitting of the singlet resonance assigned to the MeO group attached to the ring into a well-resolved pair of signals, in the 19:1 ratio ; considering that the *ee* of the used auxiliary chiral amine was 93 %, *we can therefore assume that the efficacy of the "chiral information transmission" in the corresponding process (8a→ 10a) is near to 97 %.*



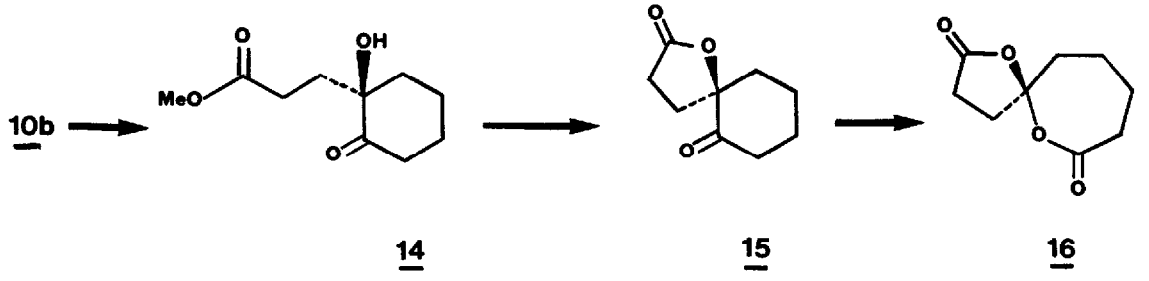
The absolute configuration of compound **9b** was unequivocally assigned by correlation with the known (9*R*,10*R*)-(*cis*) and (9*R*,10*S*)-(*trans*) 10-hydroxy-2-decalones **12** and **13**, both previously described by Prelog [11]. For this purpose, diketones **9** were first cyclized (**9a** : 5 % KOH in MeOH, 20 %, 12 h, 75 % yield ; **9b** : pyrrolidinium acetate, CH_2Cl_2, 20 °C, 15 h, 75 % yield) into octalones **11** [12]. One should note that the aforementioned conditions of cyclization are crucial, more drastic conditions giving mainly tetrahydronaphthol derivatives.

Octalone **11b** was then hydrogenated (3 bars of hydrogen, $Pd(OH)_2$; in these conditions, the desired hydrogenolysis of the benzyl group occured simultaneously), giving quantitatively an equimolar mixture of *cis* and *trans* hydroxy-decalones **12** [13] and **13** [14], easily separated by flash chromatography. The physical and spectral data of these decalones (mp, specific optical rotations, IR spectra) were in complete agreement with those published by Prelog. This correlation sequence ascertains the *R* configuration of compound **9b** ; consequently, the predominant approach to the incoming electrophile in the corresponding Michael addition process (**8b** → **9b**) was *synplanar* to the methyl group borne by the chiral amine component of the starting imine (assuming that the latter reacted in its energetically preferred conformation, depicted in Fig. **8b**), a stereochemical outcome in agreement with our previous findings [6].



a R = Me **b** R = Bn

The essential features of the present process having been established, we turned then to the conversion of product **10b** into the target oxa-spiro derivatives **15** and **16**. To this end, the benzyl group of compound **10b** was first cleaved (3 bars of hydrogen, $Pd(OH)_2$), and the resulting hydroxy-ester **14** was next saponified (1 % NaOH in MeOH-THF), giving an hydroxy-acid which spontaneously cyclized into the expected (*R*) spirolactone **15** [15] (75 % overall yield). Finally, a Baeyer-Villiger oxidation of compound **15** (1 eq of MCPBA, CH_2Cl_2, 20 °C, 1 h : these mild operating conditions are crucial, a prolongation of the reaction ruining product **16**) led, with a high degree of regioselectivity [16], to (*R*) spiro-bislactone **16** [17] with a 85 % yield.



The transformation of spirolactones **15, 16** into corresponding spiroether and spiroketal derivatives and the extension of the present reaction, by the variation of the ring size of the starting cyclanones, or by the replacement of the oxygen atom of the alkoxy substituent by other heteroatoms (particularly nitrogen), are currently under investigation in our laboratory.

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7. Made in two steps by addition of alcohols to cyclohexene oxide (MeOH, H^+, 0 °C for **7a**, $PhCH_2ONa$, DMF, 60 °C for **7b**), followed by Jones oxidation.
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9. Silica gel chromatography of compounds **9** afforded, significant amounts of the corresponding aldols. **9b** : IR (neat) : 1720, 1715, 1450 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ : 7.35 (5H, m), 4.5 (1H, d, J=12 Hz), 4.15 (1H, d, J=12 Hz), 2.05 (3H, s), 2.8-1.3 (12H, m).
10. **10b** : $[\alpha]_D^{22}$+32.5° (c=10, EtOH) ; IR (neat) : 1740, 1720, 1450, 1435 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ : 7.35 (5H, m), 4.48 (1H, d, J=11.2 Hz), 4.15 (1H, d, J=11.2 Hz), 3.64 (3H, s), 2.75 (1H, m), 2.4-1.4 (11H, m) ; ^{13}C NMR (20.1 MHz, $CDCl_3$) δ = 20.8 (t), 26.9 (t), 27.6 (t), 27.8 (t), 37.1 (t), 39.5 (t), 51.6 (s), 65.0 (t), 82.1 (s), 127.2 (d, 2C), 127.5 (d), 128.4 (d, 2C), 138.1 (s), 174.0 (s), 211.8 (s).
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12. **11b** : $[\alpha]_D^{22}$ +106° (c=3.6, CCl_4) : IR (neat) : 1680, 1630, 1450 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ : 7.4 (5H, m), 5.9 (1H, d, J=1.5 Hz), 4.5 (1H, d, J=12 Hz), 4.3 (1H, d, J=12 Hz), 2.8-1.3 (12H, m) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ : 21.0 (t), 27.5 (t), 30.8 (t), 32.5 (t), 34.7 (t), 37.1 (t), 64.1 (t), 74.1 (s), 126.1 (d), 128.9 (d, 2C), 127.2 (d), 128.2 (d,2C), 138.6 (s), 164.0 (s), 198.6 (s).
13. **12** : mp 75-76 °C (hexane) ; $[\alpha]_D^{22}$ +8.5° (c=4, EtOH) ; IR (KBr) : 3400, 1705, 1450 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ : 3.15-2.8 (2H, m), 2.8-1.0 (14H, m) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ : 23.5, 25.1, 30.4, 32.6, 36.9, 39.5, 43.3, 45.7, 70.6, 212.0 (lit. [11] : mp 78 °C ; $[\alpha]_D$ −9° [EtOH] (9S,10S enantiomer).)
14. **13** : mp 108-109 °C (cyclohexane) ; $[\alpha]_D^{22}$ +31.5° (c=4.1 EtOH) ; MS (70 eV) m/e : 168 (M^+), 150, 111, 108, 98 ; IR (neat) : 3400, 1700 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ : 3.05-2.5 (2H, m), 2.5-1.2 (14H, m) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ : 21.2 (t), 25.1 (t), 28.6 (t), 37.3 (t), 38.5 (t), 39.6 (t), 43.87 (d), 43.93 (t), 66.7 (s), 211.8 (s) (lit. [11] : mp 112 °C ; $[\alpha]_D$ −34° [EtOH] (9S,10R enantiomer).)
15. **15** : mp 82-84 °C (ether) ; $[\alpha]_D^{22}$ −44° (c=6, AcOEt) ; MS (70 eV) m/e : 168 (M^+), 124, 111, 98, 83 ; IR (KBr) : 1775, 1715, 1450 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ : 2.8-2.4 (5H, m), 2.2 (1H, m), 2.1-1.7 (6H, m) ; ^{13}C NMR (20.1 MHz, $CDCl_3$) δ : 21.57 (t), 26.82 (t), 28.1 (t), 28.7 (t), 38.8 (t), 39.2 (t), 88.3 (s), 175.5 (s), 205.9 (s).
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17. **16** : mp 88-90 °C (ether) : $[\alpha]_D^{22}$ +32.5° (c=1.4, CCl_4) ; MS (CI, NH_3) m/e : 202 ($M^+ + NH_4^+$), 185 ($M^+ + H^+$), 167, 74 ; IR (KBr) : 1800, 1740 cm^{-1} ; ^{13}C NMR (20.1 MHz, $CDCl_3$) δ : 22.7 (t), 23.7 (t), 27.3 (t), 36.2 (t), 36.6 (t), 37.9 (t), 108.5 (s), 173.0 (s), 174.7 (s).

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