Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 8, pp. 1433-1434, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00200-2

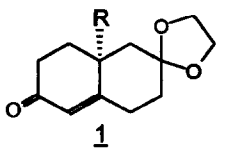
ENANTIOSELECTIVE SYNTHESIS OF SUBSTITUTED OCTALONES

Lúcia C. Sequeira[a,b] ; Paulo R. R. Costa[b*] ; Alexandre Neves[b] and Pierre Esteves[a]

a) Instituto de Química b) Núcleo de Pesquisas de Produtos Naturais - Universidade Federal do Rio de Janeiro 21941 , Cidade Universitária (CCS - Bloco H) , Rio de Janeiro , R. J. , Brasil

Abstract: *The octalones (R)-(-)-1a and (S)-(-)-1b were prepared from the Michael adducts 7a and 7b respectively. These intermediates were obtained by the "deracemizing alkylation" of cyclanones 3a and 3b .*

As part of a program aimed at the synthesis of terpenoids isolated from Brazilian plants, we needed to prepare the octalones 1a-b in high enantiomeric purity. In this paper, we describe the enantioselective synthesis of these octalones, using the "deracemizing alkylation of chiral imines"[1] as the key step to introduce the chirality. Both the operational simplicity and the recovery of the chiral auxiliary make this method one of the most attractive for the enantioselective construction of quaternary stereogenic centers.

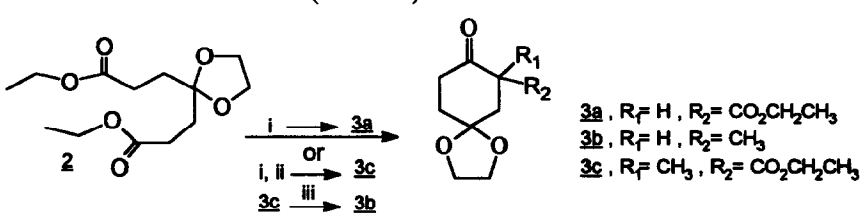


1

a, R= $CO_2CH_2CH_3$
b, R= CH_3

The starting materials, the cyclohexanones 3a-b were prepared from available diethyl γ-ethylenedioxypimelate 2, obtained from furfural[2]. It has been demonstrated that the generation of cyclic β-ketoesters by Dieckmann condensations is promoted by the use of potassium in toluene under sonication[3]. Using Luche's conditions[3], 2 was transformed into 3a in 30-40 min. at room temperature in 80-85% yield. In addition, the trapping of the K-enolate intermediate with methyl iodide (in a one pot procedure) also led to 3c in good yield (80-85%), giving, after descarboxylation, 2-methylcyclanone 3b (75-80%) (Scheme 1).

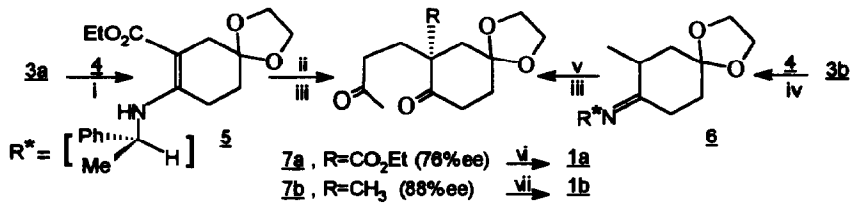
(Scheme 1)



(i: K/toluene - ultrasound ; ii: CH_3I ; iii: KOH 10%(aq.)/EtOH- refl.(16h))

Compounds 3a and 3b were allowed to react with (S)-(-)-phenylethylamine 4 (89% ee), respectively, leading to the enamine 5[4] and imine 6[1]. These chiral intermediates were alkylated with methylvinylketone (MVK), furnishing, after hydrolytic work-up, the corresponding Michael adducts 7a[5] and 7b[6] (Scheme 2).

(Scheme 2)



(i: benz. refl. 14h ; ii: MVK / $ZnCl_2$ / THF ; iii: 10%AcOH ; iv: toluene (TsOH cat.) ;refl 6h ; v: MVK / THF ; vi: EtONa / EtOH ; vii: MeONa / MeOH)

The enantiomer of 7a was previously prepared by Hermann and Wynberg[7] in 20% ee and transformed by these authors into its octalone. We achieved 7a using the conditions described by Guingant[4] in 76% ee, estimated from ^1H NMR, run in the presence of [Eu(hfc)$_3$] as chiral shift reagent. In the same way, Michael adduct 7b was prepared in 88% ee. While we were developing our work, a synthesis of the enantiomer of 7b, using the same methodology as ours, was reported[8]. Treatment of (R)-(-)-7a and (S)-(+)-7b with sodium alkoxide led to the desired octalones (R)-(-)-1a[9] and (S)-(-)-1b[10], already used in racemic forms as starting materials for the preparation of racemic natural products. The synthesis of terpenes isolated from Brazilian plants using these octalones are under investigation in our laboratory.

References and Notes :

1) d'Angelo, J. ; Desmaele, D. ; Dumas, F. and Guingant, A. *Tetrahedron : Asymmetry* , **1992** , **3** , 459
2) Narang, S. A. and Dutta, P.C. *J. Chem. Soc.* , **1960** , 2842
3) (a)Einhorn, C. ; Einhorn, J. and Luche, J. L. *Synthesis* , **1989** , 782 (b) note: Ultrasonic irradiation were realized using a common cleaning bath (Thornton T-14)
4) Guingant, A. and Hammami, H. *Tetrahedron : Asymmetry* , **1991** , **2** , 411
5) **(R)-(-)-7a** (77% yield) colorless oil(bulb to bulb distillation - 120° / 2.25 mm); $[\alpha]_D$ = - 36 (c=3 ; CCl_4)[7] (76% ee , by NMR with [Eu(hfc)$_3$]); ^1H NMR (200Mz, $CDCl_3$) δ (ppm): 4.35-4.09(m,2H) 4.09-3.90(m,4H) 3.15-1.70(several absorptions,10H) 2.13(s,3H) 1.29(t,3H,J=7.4Hz).
6) **(S)-(+)-7b** (71%) pale yellow oil (bulb to bulb distillation - 120° / 0.6 mm); $[\alpha]_D$ = +4.6 (c=2.8,CCl_4) (88%ee, by NMR with [Eu(hfc)$_3$]); ^1H NMR(200Mz, $CDCl_3$) δ(ppm): 4.0(broad unresolved multiplet,4H) 2.70-1.60(several absorptions, 10H) 2.15(s,3H) 1.13(s,3H).
7) Hermann,K.and Wynberg,H. *J. Org. Chem.* , **1979** , **44** , 2238
8) Pfau, M. ; Jabin,I. and Revial,G. *J.Chem.Soc.Perkin Trans I* , **1993** , 1935
9) **(R)-(-)-1a** colorless oil (bulb to bulb dist. - 145° / 1.0 mm); $[\alpha]_D$ = - 108 (c=0.5,CCl_4) ^1H NMR (200Mz,$CDCl_3$) δ(ppm): 6.01(d,1H,J=2Hz) 4.35-4.10(m,2H) 4.10-3.85(m,4H) 3.05-1.49(several absorptions, 10H) 1.28(t,3H,J= 6.3 Hz).
10) **(S)-(-)-1b** colorless oil (bulb to bulb dist.- 122° / 0.8 mm) $[\alpha]_D$ = - 171 (c=0.9, CCl_4) ^1H NMR (200Mz,$CDCl_3$) δ(ppm): 5.80(br. s, 1H) 4.10-3.90(m,4H) 2.80-1.50(several absor.,10H) 1.35(s, 3H).

(*Received in UK* 20 *May* 1994; *accepted* 30 *June* 1994)