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Reaction of Phenylacetate Enolates with γ- bromo α,β-Unsaturated Derivatives: Diastereo-and Enantioselective Allylic Substitution

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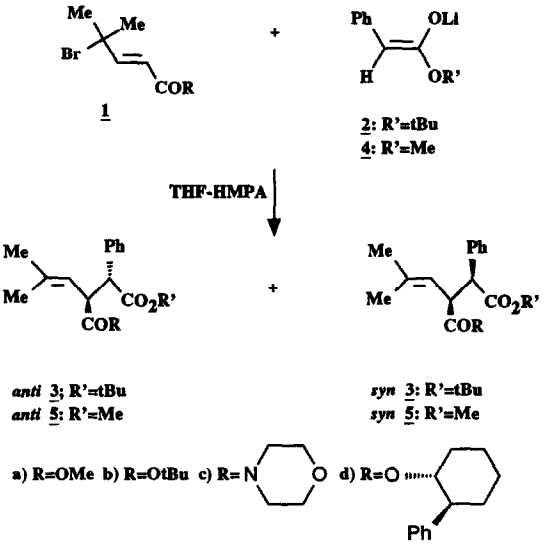
Abstract: The reaction of Li t.butyl phenylacetate enolate with γ-bromo-α,β-unsaturated esters 1a,b is regio-and stereoselective. Asymmetric synthesis can be performed with a chiral ester 1d. With amide 1c, the regio-and stereoselectivity are poor.

We have recently studied[1a,b] the reaction of some carbon nucleophiles with a tertiary γ-bromo α,β-unsaturated ester 1a and found that, in THF-HMPA, a highly regioselective allylic substitution with transposition (S_N') was taking place.

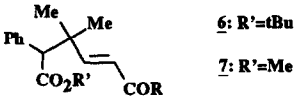
1a

Moreover, when the nucleophile was Li t.Bu phenylacetate enolate 2[2], the reaction was highly stereoselective[1b], the ***anti*** isomer 3a being predominantly formed (de=80%).

In this paper, we examine the scope of this reaction by varying the substituent on the electrophile: reaction of a bulky t.Bu ester 1b with t.Bu or Me phenylacetate enolates 2 and 4, of an amide 1c with 2 and finally of a chiral ester 1d with 2, in order to perform an asymmetric synthesis[1c].



The reaction of t.Bu 4-bromo-4-methylpent-2-enoate **1b** with lithiated t.Bu phenylacetate enolate **2** in THF-HMPA was regio and stereoselective, ***anti*** **3b** being predominantly obtained (de=92%) provided that it was run under kinetic control, i.e. below -40°C, as, at higher temperature some epimerization took place, the amount of ***syn*** **3** increasing. A similar result was obtained when reacting **1b** with the methyl ester analog, leading thus to ***anti*** **5** (de=80%). In these two cases, a small amount of non transposed S_N isomer **6b** and **7b** was also formed (≤ 10%).



All these assignments rely on IR, ^1H and ^{13}C NMR determinations as well as on microanalysis of solid compounds. The ***anti/syn*** assignments are done as previously proposed[1b] by comparison of the vinylic Me chemical shifts in each couple of diastereoisomers.

When the reaction was performed from α,β-unsaturated amide **1c** and enolate **2**, a mixture of ***anti*** **3c**, ***syn*** **3c** and **6c** in a 44/24/32 ratio at r.t. or 53/18/28 ratio at -60°C was obtained. Similarly, from **1c** and enolate **4**, ***anti*** **5c**, ***syn*** **5c** and **7c** were formed in a 45/25/30 ratio at r.t. or 62/16/22 ratio at -60°C[3]. As such a poor regioselectivity might be due to a change in mechanism [1a], the reaction was run in the presence of radical traps: p.dinitrobenzene or 4,4,6,6-tetramethylpiperidine-N-oxide. No change in products ratios or yields was observed.

From these results, it appeared that there was no chance to perform any asymmetric synthesis using chiral amides as substrates. Therefore, using Li t.Bu phenylacetate enolate **2**, the reaction of which being

more stereoselective, we selected a chiral γ-bromo-α,β-unsaturated ester which, under its s-*cis* *syn* favored conformation[4], should present one of the face of the double bond sufficiently hindered to prevent its attack. The *trans* 2-phenylcyclohexylester[5] seemed suitable as, by molecular modeling (Alchemy on IBM PC), the phenyl ring was lying over one face of the double bond (Fig.I). The ^{1}H NMR of 1d confirms such a favored conformation as the vinylic protons are shielded by the phenyl group, related to 1a, the upfield shift being 0.26 ppm for both protons.

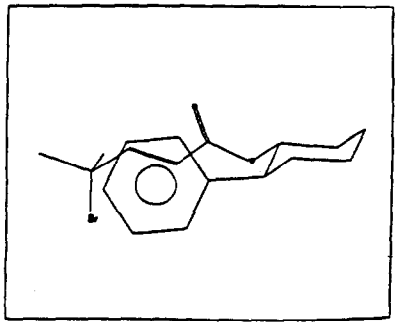


Fig.I. Favored conformation of ester 1d

The stereochemical results fulfilled our expectations: the reaction of 2 with racemic or enantiomerically pure (1'R, 2'S) 1d was regio-(75%) and stereoselective (de≥95%): *anti* 3d was obtained by fractionate crystallization (isolated yield 60-65%). No *syn* 3d could be detected either by ^{13}C NMR or ^{1}H NMR in the presence of Eu(fod)$_3$ of the crude reaction mixture. The ^{1}H NMR spectra of racemic *anti* 3d and of the compound obtained from enantiomerically pure (1'R, 2'S) 1d in the presence of Eu D-3-heptafluorobutylcamphorate showed that the ee of the latter was ≥ 95%.

A single crystal, suitable for X-ray crystallographic determination, was obtained from the racemate. This diffractometric analysis (Fig.II, Fig.III and Table I) showed the relative configuration of the chiral centers as being (2S*, 3S*, 1'R*, 2'S*), inferring thus the (2S, 3S, 1'R, 2'S) configuration of *anti* 3d pure enantiomer and the attack of the Re face of the double bond in (1'R, 2'S) 1d, the Si face being hindered by the phenyl group. This structural analysis also confirms the previously assigned *anti* relationship in the predominating isomers of 3.

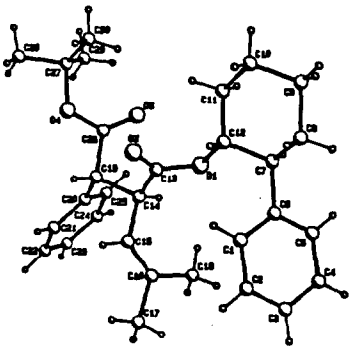


Fig.II. Molecular structure of *anti* 3d and scheme of atom numbering

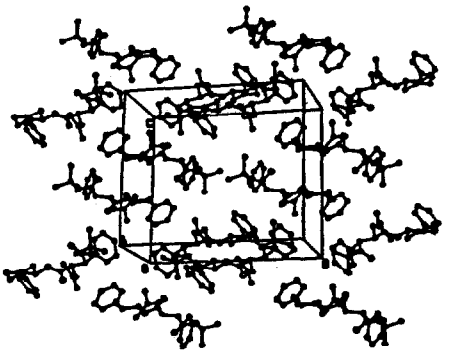
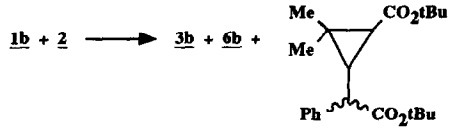


Fig.III. Crystal packing of the molecules (viewed along a) of *anti* 3d.

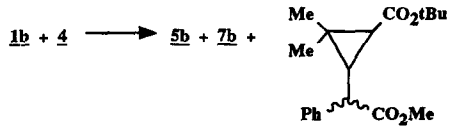
Table I. Crystallographic data for *anti* 3d

Formula	$C_{30}H_{38}O_4$
M_r	462.63
Crystal system	monoclinic
Space group	p 2_1 / n
a/Å	10.623(2)
b/Å	17.241(3)
c/Å	14.938.4(4)
α/ deg	90.
β/ deg	92.29(2)
γ/ deg	90.
V/Å^3	2733.8(1.8)
Z	4
Dc/ g cm^{-3}	1.12
F(000)	1000
μ (MoKα) / cm^{-1}	0.68
Reflections measured	5650
Unique reflections	5052
Reflections used (I≥3σ(I))	1697
R, R_ω	0.056 , 0.055

The reaction of 1b with 2 and 4 was also performed in pure THF or in THF-Et_2O with the expectation of stereoselective cyclopropane 8 or 9 formation resulting from a Michael Induced Ring Closure[1,6]: indeed, YAMAGUCHI and al.[7] observed a highly stereoselective MIRC reaction from Li t.butyl propionate enolate and ethyl 4-bromocrotonate. Literature data[8] also indicate the higher stereoselectivity observed in Michael addition of t.butyl ester enolates related to methyl or ethyl analogues. The results obtained were as disappointing as the previous ones[1b] (Table II): we also observed unselective reactions in which a mixture of *anti* and *syn* 3b or 5b, diesters 6b and 7b were obtained next to diastereoisomeric cyclopropyl diesters 8_1,8_2 and 9_1,9_2.



8_1 and 8_2



9_1 and 9_2

8 and 9 were purified by column or thick plate chromatography and identified by IR and NMR, the stereochemical assignements relying, as previously[1b] on ^1H NMR coupling constants and comparison of cyclopropyl Methyl protons chemical shifts.

Table II: Reaction of 1b with 2 and 3 in THF and THF-Et_2O.

Enolate	solvent (t°)	yield%	relative %[a]				
			anti 3b or 5b	*syn* 3b or 5b	6b or 7b	8_1 or 9_1	8_2 or 9_2
2	THF (r.t.)	80[b]	20	2	2	37	37
4	THF (r.t.)	-	29	6	11	37	18
4	THF (0°)	-	21	5	13	46	15
4	THF (-40°) / Et_2O (0°C)	no reaction					
4	THF-Et_2O (r.t.)	70[b]	28	7	10	35	21

a) determined by GPC
b) determined by ^1H NMR (toluene internal standard)

The poor regio-and stereoselectivity observed in the present case, even when using bulky ester enolate 1b strongly differs from Yamaguchi's results[7]. These facts can be assigned, as previously proposed[1b], to the difference in structure of both enolates used: poorly charge delocalized in t.butyl propionate enolate, strongly delocalised into the phenyl ring in 2 and 4[2].

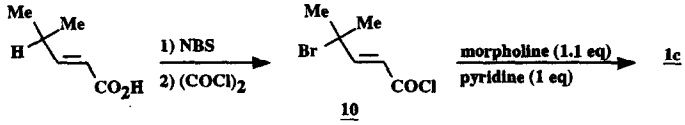
In conclusion, the reaction of lithiated phenylacetate enolates 2 and 4 with tertiary γ-bromo α,β unsaturated esters and amide 1 is regioselective in THF-HMPA, towards S_N' products 3 and 5 only from esters. This S_N' allylic substitution can be stereoselective when using bulky esters groups on each or on both reagents at low temperature. From (1'R, 2'S) phenylcyclohexyl ester 1d, asymmetric synthesis can be performed leading to (2S, 3S, 1'R, 2'S) β,γ-unsaturated diester 3d. The chiral auxiliary can be removed by LAH reduction[1c].

EXPERIMENTAL PART

All the solvents and bases were used as previously described[1], as well as the analytical and spectroscopic equipments. Bromoesters 1a and 1b as well as t.butyl phenylacetate were prepared as previously[1b]. (1R*, 2S*) and (1R, 2S) phenylcyclohexanol were purchased from Fluka and used as received.

(*E*) N-Morpholinocarbonyl-3-bromo-3-methylbut-1-ene 1c

It was prepared according to the following scheme[9]:



a) To a NBS suspension (8 g, 45 mmoles) in CCl_4 (40 ml), 4-methylpent-2-enoic acid (5 g, 44 mmoles) were added. The mixture was heated to 80°C for 2 hrs. After cooling, succinimide was filtered and washed with CCl_4. After evaporation of the solvent, the raw bromoacid was dissolved in CH_2Cl_2 (40 ml) and treated at r.t. by oxalyl chloride (5 ml, 50 mmoles). After 12 hrs stirring, the excess of $(COCl)_2$ was evaporated under reduced pressure, the residue was dissolved in pentane. The organic phase was filtered and distilled under reduced pressure. Acid chloride 10 was obtained in 66% yield as a liquid (Eb/3=62°C). 10: IR: (ν_{max}, cm^{-1}): 3000, 1775, 1640; NMR: ^1H ($CDCl_3$, 200 MHz) δ: 7.31 (d, J=15.3 Hz, 1 H); 6.12 (d, J=15.3 Hz, 1H); 1.94 (s, 6 H); M.S. (I.C. NH_3): m/z=209 (4); 177 (54); 175 (45); 131 (44); 114 (100).

b) To a solution of acid chloride 10 (3.54 g, 16.7 mmoles) in anhydrous toluene (53 ml), a solution of pyridine (1.35 ml, 16.7 mmoles) and morpholine (1.6 ml, 18.4 mmoles) in toluene (11 ml) was added at -78°C and stirred for 2 hrs. The mixture was warmed up to r.t., the formed salt filtered and washed with ether. The organic phases were concentrated under reduced pressure and the crude product triturated with pentane: crystals were obtained which were further washed with pentane and kept below -10°C (yield 72%). Due to its poor stability, 1c was not further purified.

1c: m.p. 62-65°C; IR (ν_{max}, cm^{-1}): 3000, 2840, 1650, 1610, 1110; ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.05 (d, J=14.6 Hz, 1H); 6.3 (d, J=14.6 Hz, 1H); 3.8-3.5 (m, 8H); 1.95 (s, 6H); M.S. (I.C. NH_3) m/z=281 ($M+NH_4^+$, 54); 280 (61); 279 ($M+NH_4^+$,55); 265 (95); 264 (100); 263 (100); 262 (88); 184 (32); 183 (26); 182 (36).

(*E*) (1'R, 2'S) phenylcyclohexyl-4-bromo-4-methyl-pent-2-enoate 1d

To a solution of (1R, 2S) or (1R*, 2S*) phenylcyclohexanol (1 g, 5.67 mmoles) and DMAP (0.77 g) in anhydrous CH_2Cl_2 (14 ml) maintained at 0°C, acid chloride 10 (1.2 g, 5.67 mmoles) in CH_2Cl_2 (2 ml) was added. After 6 hrs stirring at r.t., the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography over SiO_2 (eluent: Et_2O-pentane 30/70).

(1R*, 2S*) 1d: yield 60%; m.p. 85.5-87°C (pentane); $C_{18}H_{23}O_2Br$: calc% C=61.54; H=6.60; O=9.11; found% C=61.55; H=6.53; O=8.93; IR (ν_{max}, cm^{-1}): 2930, 1705, 1640, 1100; ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.32-7.14 (5 H); 6.92 (d, J=15.6 Hz, 1H); 5.62 (d, J=15.6 Hz, 1H); 5.1-4.97 (m, 1H); 2.8-2.67 (m, 1H); 2.25-1.3 (m, 8H); 1.82 (s, 6H); M.S. (I.C. NH_3) m/z=370 (28), 291 (31), 290 (57), 273 (83), 271 (32), 159 (57), 158 (44), 132 (100), 115 (58), 108 (27).

(1R, 2S) 1d: yield 83%. oil.

General experimental procedure:

$PhCH_2COOtBu$ or $PhCH_2COOMe$ (1.5 mmoles) was dissolved in a THF (2.5 ml)-HMPA (1.5 ml) mixture or in pure THF (4 ml). LiHMDS 1 M (1.7 ml, 1.7 mmoles) was added at r.t. After 15 mn stirring, the mixture was cooled to -60°C and the bromo derivative 1 (1.5 mmoles in 1 ml THF) slowly added. The mixture was stirred until the starting material was consumed (followed by GC). A saturated aqueous NH_4Cl solution was then added and the organic compounds extracted by CH_2Cl_2. After washing with brine, the organic phase was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The residue was dissolved in AcOEt-pentane 1/1 and filtered through a small silica gel column to remove HMPA when necessary. It was then analysed by capillary GLC and ^1H NMR. The products were crystallized or purified by column or thick plate chromatography on silica gel.

Kinetic vs thermodynamic control

To a 90/10 mixture of ***anti/syn*** 3a (***anti/syn*** 5b), 0.2 eq of 2 (4) was added at r.t. in THF-HMPA. After 30 mn stirring at r.t. and previous treatment, a nearly 1/1 mixture of ***anti/syn*** 3a (5b) was obtained as determined by capillary GLC.

Description of new compounds

Anti 3b: isolated by crystallization. yield 60%. m.p. 120-122°C (pentane). $C_{22}H_{32}O_4$: calc% C=73.50; H=8.95; O=17.75; found% C=72.24; H=8.90; O=18.02. IR ($CHCl_3$, ν_{max}, cm^{-1}): 3000, 1740, 1370, 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.3-7.1 (5 H); 4.85-4.75 (m, 1H); 3.75-3.72 (AB part of ABX, 2H); 1.52 (d, J=1.2 Hz, 3H); 1.45 (s, 9H); 1.37 (s, 9H); 1.34 (d, J=1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 173; 172.3; 137.1; 128.4; 128.1; 126.9; 119.7; 80.7; 80.4; 54.6; 49.4; 27.9; 25.6; 18. MS m/z=360 (M^+) (0.1); 136 (20); 57 (100); 41 (20).

Anti 5b: isolated by crystallization. yield 52%. m.p. 78-79°C (pentane). $C_{19}H_{26}O_4$: calc% C=71.67; H=8.23; O=20.1; found% C=71.56; H=8.26; O=20.21. IR (CCl_4, ν_{max}, cm^{-1}): 3000, 1740, 1720, 1370, 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.2-7.1 (5H); 4.8-4.7 (m, 1H); 3.8-3.74 (m, 2H); 3.57 (s, 3H); 1.44 (s, 3H); 1.37 (s, 9H); 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 173.5; 172.7; 137.5; 128.5; 128.3; 127.3; 119.4; 80.7; 53.5; 52.1; 49.3; 27.9; 25.6; 18.5. MS m/z=157 (24); 150 (48); 113 (10); 69 (13); 57 (100), 41 (31).

Syn 5b: isolated by flash chromatography. yield 4%. m.p. 110-112°C (pentane). $C_{19}H_{26}O_4$: calc%

C=71.67; H=8.23; O=20.1; found% C=71.01; H=8.14; O=20.5. IR (CCl_4, ν_{max}, cm^{-1}): 2970, 1740, 1725, 1370, 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.4-7.15 (5H); 5.07 (bd, J=9.1 Hz, 1H); 3.95-3.75 (AB part of ABX, J_{AB}=10.2 Hz, 2H); 3.53 (s, 2H); 1.76 (s, 3H); 1.74 (s, 3H); 1.1 (s, 9H). MS m/z=318 (M^+) (0.2); 157 (58); 150 (96); 113 (58); 57 (100); 41 (31).

Anti 3c: isolated by thick plate chromatography. m.p. 135-137°C. $C_{22}H_{31}O_4N$: calc% C=70.75; H=8.37; O=17.13; found% C=70.19; H=8.27; 0=16.55. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2960, 1700, 1630, 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.26-7.16 (5H); 5-4.93 (m, 1H), 3.89-3.87 (AB part of ABX, 2H); 3.8-3.3 (m, 8H); 1.5 (s, 3H); 1.37 (s, 9H); 1.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 173.6; 166.5; 137; 128.7-126.9; 119.9; 80.6; 66.9; 66.6; 54.7; 46.3; 46; 42.4; 27.8; 25.4; 17.6. MS (I.C. NH_3) m/z=374 (100); 318 (87); 182 (31).

Syn 3c: obtained in mixture with ***Anti*** 3c by thick plate chromatography in a 40/60 ratio. ^1H NMR (from the mixture, $CDCl_3$, 200 MHz): 7.4-7.1 (5H); 5.35 (dq, J=10.5 and 1 Hz, 1H); 4.2-3.9 (AB part of ABX, J_{AB}=10.5 Hz, 2H); 3.8-3.3 (m, 8H); 1.73 (d, J=1 Hz, 6H); 1.37 (s, 9H).

Anti 5c: isolated by thick plate chromatography. yield 40%. m.p. 94-96°C (Et_2O-pentane). $C_{19}H_{25}O_4N$: calc% C=68.86; H=7.60; N=4.23; found% C=68.55; H=7.46; N=4.25. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2960; 1720; 1630; 1110. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.22-7.09 (5H); 4.83 (d, J=9.9 Hz, 1H); 4-3.83 (AB part of ABX, J_{AB}=10.7 Hz, 2H); 3.72-3.34 (m, 8H); 3.59 (s, 3H); 1.44 (s, 3H); 0.95 (d, J=1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 174.2; 172.1; 136.6; 128.8-127.2; 119.6; 66.9; 66.6; 53.6; 52.1; 46.4; 46; 42.5; 25.3; 15.8. MS (I.C. NH_3) m/z= 333 (21), 332 (100), 182 (10).

Syn 5c: isolated by thick plate chromatography. Oil. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2960; 1720; 1630; 1110. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.44-7.2 (5H); 5.3 (dq, J=8.8 and 1 Hz, 1H); 4.27-4.07 (AB part of ABX, J_{AB}=10.6 Hz, 2H); 3.63 (s, 3H); 3.6-2.85 (m, 8H); 1.73 (d, J=1 Hz, 3H); 1.71 (d, J=1 Hz, 3H). MS m/z= 182 (100); 114 (21); 70 (23).

Anti 3d:

racemate isolated by fractionate crystallisation. yield 62%. m.p. 153-155°C. $C_{30}H_{38}O_4$: calc% C=77.89; H=8.28; O=13.83; found% C=77.66; H=8.21; O=13.64.

pure (2S, 3S, 1'R, 2'S) enantiomer: isolated by fractionate crystallisation. yield 60%. m.p. 148-149°C (hexane). $[\alpha]_D$ ($CHCl_3$, c=0.75): -188°5. IR ($CHCl_3$, ν_{max}, cm^{-1}): 3000; 2940; 1710; 1360; 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.26-7.7 (10H); 5.1-4.9 (m, 1H); 4.3 (bd, J=7.8 Hz, 1H); 3.75 to 3.55 (AB part of ABX, J_{AB}= 9.9 Hz, 2H); 2.8-2.6 (m, 1H); 2.25-1.21 (m, 8H); 1.34 (s, 9H); 1.19 (s, 3H); 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 173.4; 172.2; 143.1; 138.6-126; 118.7; 80.6; 75.6; 54.2; 49.5; 47.9; 34.5; 32.1; 27.7; 25.8; 25.4; 24.7; 17.5. MS (I.C. NH_3) m/z= 464 (21); 463 (43); 462 (2); 408 (34); 407 (100); 249 (18); 159 (22); 158 (24).

6c: isolated by thick plate chromatography. yield 20%. m.p. 73-75°C. $C_{22}H_{31}O_4N$: calc% C=70.75; H=8.37; N=3.75; found% C=70.76; H=8.56; N=3.46. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2960; 1720; 1650; 1610. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.4-7.2 (5H); 7.0 (d, J=14.7 Hz, 1H); 5.93 (d, J=14.7 Hz, 1H); 3.8-3.4 (m, 8H); 1.46 (s, 1H); 1.4 (s, 9H); 1.16 (s, 3H), 1.14 (s, 3H). MS (I.C. NH_3) m/z= 375 (25); 374 (52); 184 (100); 182 (60).

7c: isolated by thick plate chromatography followed by washing with hexane. Oil. IR ($CHCl_3$, ν_{max}, cm^{-1}): 3000; 1730; 1650; 1600. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.35-7.25 (5H); 6.97 (d, J=15.5 Hz, 1H); 5.95 (d, J=15.5 Hz, 1H); 3.85-3.5 (m, 8H); 3.64 (s, 3H); 1.25 (s, 1H); 1.17 (s, 3H), 1.15 (s, 3H). MS (I.C. NH_3) m/z= 332 (100); 182 (13).

6d: isolated as a 1/1 mixture of stereoisomers by thick plate chromatography. yield 8%. Oil. IR ($CHCl_3$, ν_{max}, cm^{-1}): 3000; 2940; 1720; 1710; 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.4-7.2 (10H); 7.05 (d, J=15.8 Hz, 0.5H); 6.97 (d, J=15.8 Hz, 0.5H); 5.44 (d, J=15.8 Hz, 1H); 5.16-5.0 (m, 1H); 3.4 (s, 1H); 2.84-2.68 (m, 1H); 2.3-2.16, 2.05-1.74, 1.7-1.3 (massif, 8H); 1.44 (s, 4.5H); 1.42 (s, 4.5H), 1.08 (s, 1.5H); 1.07 (s, 1.5H);

1.05 (s, 1.5H); 1.03 (s, 1.5H).

$\underline{8}_1$: isolated by thick plate chromatography. Oil. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2960; 1700; 1360; 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.4-7.3 (m, 5H); 3.16 (d, J=11.2 Hz, 1H); 2.0 (dd, J=6.7 and 11.2Hz, 1H); 1.46 (s, 9H); 1.43 (s, 9H); 1.28 (d, J=6.7 Hz, 1H); 1.24 (s, 3H); 1.07 (s, 3H). MS m/z= 157 (14); 136 (16); 118 (14); 113 (31); 57 (100); 41 (15).

$\underline{9}_1$: isolated by crystallization. m.p. 119-120°C. $C_{19}H_{26}O_4$: calc% C=71.67; H=8.23; O=20.10; found% C=71.71; H=8.22; O=19.96.

IR ($CHCl_3$, ν_{max}, cm^{-1}): 2980-2960; 1750; 1730; 1160. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.34-7.27 (m, 5H); 3.69 (s, 3H); 3.27 (d, J=11 Hz, 1H); 2.1 (dd, J=5.7 and 11 Hz, 1H); 1.38 (s, 9H); 1.29 (s, 3H); 1.25 (s, 3H); 1.19 (d, J=5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 173.7; 171; 128.6-127.2; 80.1; 52.1; 50.5; 34; 33.4; 27.5; 21.5; 20.4. MS m/z= 150 (75); 118 (47); 113 (100); 57 (42).

$\underline{9}_2$: isolated by thick plate chromatography. Oil. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2960; 1730; 1710; 1150. ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.4-7.3 (m, 5H); 3.67 (s, 3H); 3.3 (d, J=10.5 Hz, 1H); 2.08 (dd, J=4.5 and 10.5 Hz, 1H); 1.45 (s, 9H); 1.43 (d, J=4.5 Hz, 1H); 1.23 (s, 3H); 1.05 (s, 3H). MS m/z= 318 (2); 262 (14); 157 (30); 150 (100); 118 (26); 113 (55); 57 (54); 41 (18).

From the ^1H NMR spectra and according to previous results[1b], the following configurations have been assigned to these compounds:

$\underline{9}_1$ $\underline{9}_2$

X-Ray crystal Structure Analysis.

Colourless needle crystals were grown from an ether solution. Single crystal with maximum dimensions 0.09x0.10x0.23 mm^3 was mounted on an Enraf-nonius CAD4-F diffractometer and irradiated with graphite monochromatized Mo K_α radiation. Unit-cell dimensions and crystal orientation matrix were derived from least-squares refinement of setting angles of 25 reflections measured in the range $15.1 < 2\Theta < 22.0°$. Intensity data with maximum Bragg angle Θ_{max}=26° (corresponding to +h: 0/13 + k: 0/21; ±l:-18/+18) were collected at room temperature using ω-2Θ scan mode with the following conditions: ω scan width Δω=(1.00 + 0.35 tgΘ)° extended 25% on each side for background measurement, horizontal aperture (2.0 + 0.5 tgΘ)mm, vertical aperture 4 mm, prescan speed 10°/mn, σ(I)/I = 0.01, maximum time for final scan 60s. The orientation was checked every 400 reflections and maintained within 0.10°. Three reference reflections measured every hour of X-ray exposure time showed no evidence of decay (average fluctuation 0.3% over 49.9 hours). 5650 reflections were measured of which 5052 were unique (R_{int} = 0.016). Data were corrected for background, Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using MULTAN11/82 (10) and refined (on F's) by full matrix least-squares calculations initially with isotropic and finally with anisotropic thermal parameters for non H-atoms. All H atoms except three on two methyl groups were visible in difference Fourier map and they were included at idealized position (C-H = 1.0 Å, $B_H = 1.3\ B_C$) in the structure factor calculations but not refined. The final R and $R_\omega$are 0.056 and 0.055 respectively for 307 variable parameters and 1697 observed reflections ($I > 3\sigma(I)$), the minimizing function being $\Sigma\omega(\Delta F)^2$ with $\omega=[\sigma^2(F_O) + 0.04\ F_O^2]^{-1}$. In the final cycle the largest parameter shift was

(Δ/σ)max = 0.00 and the standard deviation of an observation of unit weight was 1.547. The final difference Fourier maps have highest peaks of +0.19 and -0.21 e.Å^{-3}. The atomic scattering factors used and the values of f' and f" of the anomalous dispersion effects included in the values of F_C were taken from International Tables for X-ray crystallography (11). The illustrations were made with the PLUTO program (12). All calculations were performed on a DEC Microvax II computer using SDP system of programs (13).

Final atomic coordinates parameters for non-H and H atoms are listed in Table III . Full lists of bond lengths and bond angles are given in tables IV and V, respectively. Additional material avalaible from the Cambridge Crystallographic Data Centre comprises anisotropic thermal parameters for non-H atoms and torsion angles. The molecular arrangement in the crystal viewed along is illustrated in Figure 3.

Table III. Positional Parameters

Atom	x	y	z	Atom	x	y	z
O1	0.0887(3)	0.4226(2)	0.1121(2)	C14	0.2042(4)	0.3070(2)	0.0938(3)
O2	0.0481(3)	0.3241(2)	0.2056(2)	C15	0.3250(4)	0.3091(3)	0.1510(3)
O3	- 0.0166(3)	0.2713(2)	- 0.0068(2)	C16	0.4271(4)	0.3493(3)	0.1358(3)
O4	- 0.0223(3)	0.1503(2)	0.0503(2)	C17	0.5405(5)	0.3446(4)	0.1996(4)
C1	0.2551(5)	0.5287(3)	0.2358(3)	C18	0.4400(6)	0.4038(4)	0.0580(4)
C2	0.3790(5)	0.5489(3)	0.2583(4)	C19	0.1630(4)	0.2216(2)	0.0773(3)
C3	0.4352(5)	0.6104(3)	0.2184(4)	C20	0.2561(4)	0.1816(2)	0.0189(3)
C4	0.3694(5)	0.6528(3)	0.1534(4)	C21	0.3449(4)	0.1326(3)	0.0577(3)
C5	0.2462(4)	0.6316(3)	0.1297(3)	C22	0.4372(5)	0.0993(3)	0.0073(4)
C6	0.1867(4)	0.5710(3)	0.1714(3)	C23	0.4396(5)	0.1147(3)	- 0.0830(4)
C7	0.0493(4)	0.5556(3)	0.1464(3)	C24	0.3506(5)	0.1626(3)	- 0.1234(3)
C8	- 0.0359(4)	0.6099(3)	0.1991(3)	C25	0.2579(5)	0.1955(3)	- 0.0726(3)
C9	- 0.1760(4)	0.5992(3)	0.1709(3)	C26	0.0307(4)	0.2189(3)	0.0347(3)
C10	- 0.2173(5)	0.5148(3)	0.1793(3)	C27	- 0.1560(4)	0.1353(3)	0.0209(3)
C11	- 0.1304(4)	0.4609(3)	0.1284(3)	C28	- 0.1729(5)	0.0526(3)	0.0543(5)
C12	0.0054(4)	0.4728(3)	0.1612(3)	C29	- 0.1689(5)	0.1384(4)	- 0.0800(4)
C13	0.1041(4)	0.3497(3)	0.1434(3)	C30	- 0.2398(5)	0.1918(4)	0.0674(4)
H1	0.2125	0.4851	0.2662	H17C	0.5606	0.3949	0.2266
H2	0.4250	0.5168	0.3036	H18A	0.3641	0.4068	0.0184
H3	0.5210	0.6222	0.2391	H18B	0.4531	0.4587	0.0774
H4	0.4111	0.6958	0.1243	H18C	0.5084	0.3928	0.0202
H5	0.1993	0.6594	0.0808	H19	0.1628	0.1954	0.1362
H7	0.0398	0.5647	0.0817	H21	0.3404	0.1205	0.1216
H8A	- 0.0102	0.6631	0.1916	H22	0.5022	0.0652	0.0360
H8B	- 0.0238	0.5981	0.2624	H23	0.5021	0.0904	- 0.1196
H9A	- 0.1902	0.6150	0.1088	H24	0.3509	0.1756	- 0.1880
H9B	- 0.2295	0.6322	0.2057	H25	0.1898	0.2280	- 0.1006
H10A	- 0.3039	0.5071	0.1593	H28A	- 0.2564	0.0316	0.0434
H10B	- 0.2127	0.4995	0.2426	H28B	- 0.1148	0.0164	0.0286
H11A	- 0.1395	0.4707	0.0649	H28C	- 0.1570	0.0479	0.1199
H11B	- 0.1551	0.4059	0.1358	H29A	- 0.1568	0.1900	- 0.1013
H12	0.0069	0.4632	0.2260	H29B	- 0.1006	0.1070	- 0.1055
H14	0.2175	0.3312	0.0360	H29C	- 0.2453	0.1184	- 0.1038
H15	0.3248	0.2760	0.2054	H30A	- 0.2308	0.1870	0.1324
H17A	0.5294	0.3091	0.2474	H30B	- 0.2171	0.2442	0.0532
H17B	0.6159	0.3290	0.1694	H30C	- 0.3270	0.1849	0.0515

Table IV: Bond Distances in Angstroms

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
C1	H1	0.996(5)	C11	H11B	0.990(5)	C23	H23	0.971(5)
C2	H2	0.988(5)	C12	H12	0.983(4)	C24	H24	0.993(5)
C3	H3	0.973(5)	C14	H14	0.973(4)	C25	H25	0.995(5)
C4	H4	0.976(6)	C15	H15	0.993(4)	C28	H28A	0.966(6)
C5	H5	0.991(5)	C17	H17A	0.952(6)	C28	H28B	0.967(6)
C7	H7	0.981(4)	C17	H17B	0.973(5)	C28	H28C	0.991(7)
C8	H8A	0.966(5)	C17	H17C	0.978(6)	C29	H29A	0.956(6)
C8	H8B	0.971(5)	C18	H18A	0.983(6)	C29	H29B	0.993(6)
C9	H9A	0.973(5)	C18	H18B	0.999(7)	C29	H29C	0.940(6)
C9	H9B	0.971(5)	C18	H18C	0.957(6)	C30	H30A	0.975(6)
C10	H10A	0.966(5)	C19	H19	0.990(4)	C30	H30B	0.963(6)
C10	H10B	0.980(5)	C21	H21	0.980(5)	C30	H30C	0.955(5)
C11	H11A	0.963(5)	C21	H22	0.992(5)			
O1	C12	1.458(4)	C6	C7	1.516(5)	C16	C18	1.504(6)
O1	C13	1.348(5)	C7	C8	1.540(5)	C19	C20	1.511(5)
O2	C13	1.206(4)	C7	C12	1.520(5)	C19	C26	1.521(5)
O3	C26	1.194(4)	C8	C9	1.541(5)	C20	C21	1.377(5)
O4	C26	1.335(4)	C9	C10	1.527(6)	C20	C25	1.389(5)
O4	C27	1.492(4)	C10	C11	1.533(6)	C21	C22	1.384(6)
C1	C2	1.390(6)	C11	C12	1.519(5)	C22	C23	1.377(6)
C1	C6	1.389(5)	C13	C14	1.512(5)	C23	C24	1.376(6)
C2	C3	1.366(6)	C14	C15	1.514(5)	C24	C25	1.388(6)
C3	C4	1.382(6)	C14	C19	1.552(5)	C27	C28	1.524(6)
C4	C5	1.391(6)	C15	C16	1.316(5)	C27	C29	1.509(6)
C5	C6	1.382(5)	C16	C17	1.508(5)	C27	C30	1.507(6)

Numbers in brackets are estimated standard deviations in the least significant digits

Table V: Bond Angles in Degrees

C12-O1-C13	116.5(3)	O1-C12-C7	106.8(3)	C19-C20-C25	121.7(4)	C6-C1-H1	118.6(5)
C26-O4-C27	120.3(3)	O1-C12-C11	110.2(3)	C21-C20-C25	118.9(4)	C1-C2-H2	117.7(5)
C2-C1-C6	120.1(4)	C7-C12-C11	111.9(3)	C20-C21-C22	120.9(4)	C3-C2-H2	121.4(5)
C1-C2-C3	121.0(5)	O1-C13-O2	123.5(4)	C21-C22-C23	119.7(5)	C2-C3-H3	116.4(5)
C2-C3-C4	120.0(5)	O1-C13-C14	111.1(4)	C22-C23-C24	120.3(5)	C4-C3-H3	123.7(5)
C3-C4-C5	119.0(5)	O2-C13-C14	125.3(4)	C23-C24-C25	119.8(5)	C3-C4-H4	119.2(5)
C4-C5-C6	121.7(4)	C13-C14-C15	108.0(3)	C20-C25-C24	120.3(4)	C5-C4-H4	121.8(5)
C1-C6-C5	118.2(4)	C13-C14-C19	109.9(3)	O3-C26-O4	126.1(4)	C4-C5-H5	120.1(5)
C1-C6-C7	123.4(4)	C15-C14-C19	109.8(3)	O3-C26-C19	123.8(4)	C6-C5-H5	118.2(4)
C5-C6-C7	118.4(4)	C14-C15-C16	126.9(4)	O4-C26-C19	110.1(4)	C6-C7-H7	105.9(4)
C6-C7-C8	110.3(3)	C15-C16-C17	120.4(4)	O4-C27-C28	100.9(4)	C8-C7-H7	111.5(4)
C6-C7-C12	115.3(3)	C15-C16-C18	124.3(4)	O4-C27-C29	109.6(4)	C12-C7-H7	105.9(4)
C8-C7-C12	107.8(3)	C17-C16-C18	115.3(4)	O4-C27-C30	109.0(4)	C7-C8-H8A	110.1(4)
C7-C8-C9	111.6(4)	C14-C19-C20	109.8(3)	C28-C27-C29	110.6(5)	C7-C8-H8B	108.3(4)
C8-C9-C10	111.6(4)	C14-C19-C26	110.2(3)	C28-C27-C30	111.9(4)	C9-C8-H8A	110.9(4)
C9-C10-C11	110.9(4)	C20-C19-C26	111.0(3)	C29-C27-C30	114.0(4)	C9-C8-H8B	109.3(4)
C10-C11-C12	109.9(4)	C19-C20-C21	119.3(4)	C2-C1-H1	121.4(5)	H8A-C8-H8B	106.5(4)
C8-C9-H9A	109.8(4)	C9-C10-H10A	112.2(5)	C10-C11-H11A	110.0(4)	O1-C12-H12	114.2(4)
C8-C9-H9B	111.3(4)	C9-C10-H10B	109.3(4)	C10-C11-H11B	110.8(4)	C7-C12-H12	108.0(4)
C10-C9-H9A	108.1(4)	C11-C10-H10A	110.5(5)	C12-C11-H11A	110.5(4)	C11-C12-H12	105.8(4)
C10-C9-H9B	109.8(4)	C11-C10-H10B	108.0(4)	C12-C11-H11B	110.3(4)	C13-C14-H14	110.8(4)
H9A-C9-H9B	105.9(5)	H10A-C10-H10B	105.7(5)	H11A-C11-H11B	105.2(4)	C15-C15-H14	109.9(4)

Table V (cont): Bond Angles in Degrees

C19-C14-H14	108.5(4)	C16-C18-H18A	113.6(6)	C20-C21-H21	118.8(4)	C24-C25-H25	121.4(4)
C14-C15-H15	114.9(4)	C16-C18-H18B	112.5(5)	C22-C21-H21	120.3(4)	C27-C28-H28A	114.5(5)
C16-C15-H15	118.1(4)	C16-C18-H18C	115.3(6)	C21-C22-H22	120.5(5)	C27-C28-H28B	112.8(5)
C16-C17-H17A	112.9(5)	H18A-C18-H18B	103.1(6)	C23-C22-H22	119.8(5)	C27-C28-H28C	112.4(5)
C16-C17-H17B	111.9(5)	H18A-C18-H18C	106.3(5)	C22-C23-H23	120.7(5)	H28A-C28-H28B	106.7(6)
C16-C17-H17C	111.7(5)	H18B-C18-H18C	105.0(6)	C24-C23-H23	119.0(5)	H28A-C28-H28C	104.8(6)
H17A-C17-H17B	107.4(5)	C14-C19-H19	107.6(3)	C23-C24-H24	122.3(5)	H28B-C28-H28C	104.7(5)
H17A-C17-H17C	107.0(6)	C20-C19-H19	109.3(4)	C25-C24-H24	117.9(5)	C27-C29-H29A	111.0(5)
H17B-C17-H17C	105.3(5)	C26-C19-H19	108.9(4)	C20-C25-H25	118.2(4)	C27-C29-H29B	109.1(5)
						C27-C29-H29C	114.1(5)

Numbers in brackets are estimated standard deviations in the least significant digits

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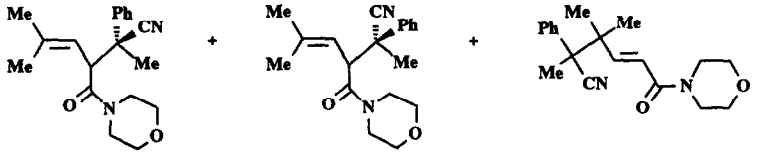

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