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γ-Amino-β-ketosulfones as Chiral Educts : A Facile Synthesis of Enantiopure α-Amino Ketones[#]

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Abstract: Starting from 'chiral-pool' derived γ-amino-β-ketosulfones, a facile synthesis of enantiopure α-amino ketones has been developed *via* an α-alkylation-desulfonation sequence. Extension of this methodology to enantiopure α-acetoxy ketone synthesis,however, have met with limited success.

Interest in the synthesis of enantiopure α-amino ketones has grown significantly in the last decade, especially due to the increasing utility of such ketones, *via* hydride reductions, in the stereoselective synthesis of homochiral 1,2-amino alcohols.[1] Although, organometallic additions to chiral-pool derived α-amino aldehydes[2] is the usual route to homochiral 1,2-amino alcohols, of late, their synthesis *via* hydride reductions of enantiopure α-amino ketones has gained considerable attention, not only because it offers a stereocomplementary strategy but also because it avoids the handling of chemically sensitive and racemization prone α-amino aldehydes. Enantiopure α-amino ketones also serve as immediate synthetic precursors to a wide variety of heterocyclic natural products and pharmaceutical agents.[3] Moreover, a number of them show significant biological activities, some of which are pertinent to AIDS chemotherapy.[4] In view of these, there is a growing need for a broad synthetic repertoire that would provide easy access to a wide variety of enantiopure α-amino ketones.

Enantiopure α-amino ketones are usually prepared *via* nucleophilic aminoacylation of organolithium and Grignard reagents (usually used in excess) with activated α-amino acid derivatives (mixed anhydrides, Weinreb-amides);[5] direct aminoacylation with Tos-amino acids is also possible but requires a large excess of the organometallic reagents.[6] However, due to difficulties in preparing organolithium reagents having functional groups, these procedures are not particularly suitable for the synthesis of functionalized α-amino ketones. The use of a large excess of the organometallic reagent is a further deterrent especially when its organic residue is valuable and requires elaborate preparative steps. Enolate alkylation of α-amino methyl ketones offers a potential solution to the above difficulties. However, surprisingly, such a strategy has so far remained largely neglected, perhaps due to the equilibration problems often encountered during enolization of such ketones.[7] Thus, apart from a handful of recent reports on aldol reactions of a L-Phe derived N,N-dibenzyl α-amino methyl ketone[8] and bromoester alkylation of a L-Phe derived γ-amino-β-ketoester,[9] nothing especially is known on this enolate alkylation strategy. With a view to develop a general and more efficient synthesis of enantiopure α-amino ketones, especially those having functionalized keto residues, we decided to investigate this enolate alkylation strategy in some more details using the chiral-pool derived γ-amino-β-ketosulfones[10] as the test substrates. Our results towards these ends are described in this paper.

[#] ***Dedicated, with profound respect and admiration, to Professor A. R. Katritzky on his 70th birthday.***

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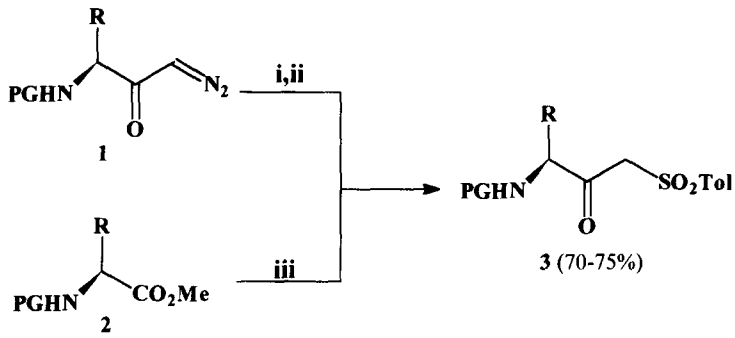
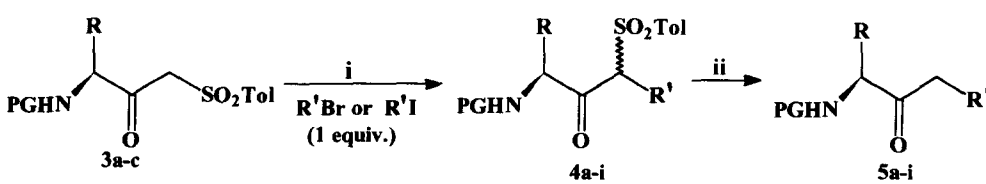
γ-Amino-β-ketosulfones are a new class of chiral educts. The existing literature provided only one report by Lygo and Rudd[11] on the utility of chiral-pool derived γ-amino-β-ketosulfones in the synthesis of ethyledine dipeptide isosteres. In the present work, the key γ-amino-β-ketosulfones **3a-c** were prepared in good yields either from the chiral-pool derived γ-amino-α-diazoketones **1a-c**[12] *via* sequential treatment with 47% HBr (ether, 0°) and $NaSO_2Tol$ (DMF, RT)[13] or *via* condensation[11] of excess α-lithio methyl tolyl sulfone with the amino acid esters **2a-c (Scheme 1)**.



PG = CO_2Et
a: R = Me; **b**: R = i-Bu; **c**: R = Bn

Scheme 1. i) 47% HBr, ether, 0°; ii) $NaSO_2Tol$, DMF, RT; iii) Li_2CHSO_2Tol, THF, -78°.

α-Alkylations of γ-amino-β-ketosulfones **3** were screened under a variety of conditions (NaH/DMF, NaH/DMSO, KOBu-t/THF, Triton-B/CH_2Cl_2-H_2O) which, however, gave incomplete conversions. Eventually, K_2CO_3 in DMF, the conditions described by Lygo in bromoester alkylation of such synthons,[11] produced the best results. Thus, reactions of **3a-c** with one equivalent of the electrophile (R ' Br) in the presence of K_2CO_3 in DMF at RT smoothly gave rise to the monoalkylated β-ketosulfones **4a-f** as a 50:50 mixture of diastereoisomers. A wide range of electrophiles including alkyl iodides (including those having functional groups), benzyl and allyl bromides can be used in this alkylation reaction to afford uniformly good yields (65-83%) of the monoalkylated products under mild reaction conditions (**Scheme 2, Table 1**). However, care must be taken during monoalkylations with allyl bromide, since use of a slight excess of this alkylating agent resulted in a considerable amount of the α,α-diallylated products (*vide infra*). Interestingly, α-monoalkylation *via* Michael reaction is also possible under the same conditions as shown by the reaction of **3c** with ethyl acrylate (**entry 6, Table 1**). However, attempted monoalkylation of **3** with MeI has invariably produced the α,α-dialkylated products. Subsequent desulfonation of **4a-f** was best achieved with Al(Hg) in refluxing 10% aqueous THF (superior to Na(Hg), Zn/HOAc or Zn/NH_4Cl) to produce the respective α-amino ketones **5a-f** in good yields (**Scheme 2, Table 1**). The product **5c**, prepared in high overall yield, is particularly valuable since it is the key intermediate for the synthesis of both ketomethylene as well as the hydroxyethylene dipeptide isosteres.[4c]



PG = CO_2Et

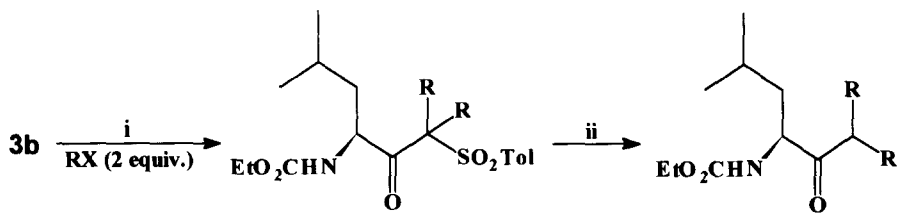
Scheme 2. i) K_2CO_3, DMF, RT; ii) Al(Hg), THF-H_2O (9:1), reflux.

Table 1. Synthesis of Enantiopure α-Amino Ketones **5** (**Scheme 1**).

Entry	3	R'	4 (yield %)	5 (yield %)
1	**3a**	$(CH_2)_4OPiv$[a]	**4a** (75)	**5a** (68)
2	**3b**	$CH_2CH{=}CH_2$	**4b** (80)	**5b** (65)
3	**3c**	CH_2CO_2Et	**4c** (72)	**5c** (74)
4	"	$CH_2CH{=}CH_2$	**4d** (83)	**5d** (60)
5	"	CH_2Ph	**4e** (68)	**5e** (50)
6	"	$(CH_2)_2CO_2Et$[b]	**4f** (65)	**5f** (70)

[a] using $I(CH_2)_4OPiv$; [b] using ethyl acrylate

α,α-Dialkylation of **3** was also carried out *e.g.* with the *L*-Leu derived β-ketosulfone **3b**. Thus, in presence of K_2CO_3 in DMF and two equivalents of allyl bromide or EtI as electrophiles, **3b** gave rise to the dialkylated products **6a,b** (*ca.* 80%) which upon desulfonation, again with Al(Hg), led to the structurally interesting enantiopure α-amino ketones **7a,b** bearing branched chain keto-residues (**Scheme 3**).

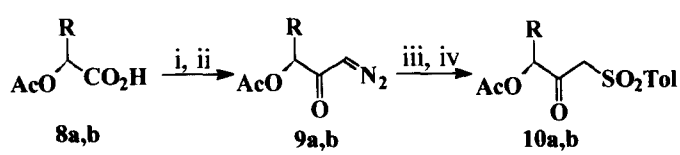


6a: R = Allyl (80%)
6b: R = Et (82%)

7a: R = Allyl (50%)
7b: R = Et (72%)

Scheme 3. i) K_2CO_3, DMF, RT; ii) Al(Hg), THF-H_2O (9:1), reflux.

Encouraged by the above success, we became interested in extending this methodology towards the synthesis of enantiopure α-hydroxy ketones.[5b] The enantiopure γ-acetoxy-β-ketosulfones (**10a,b**), required for this purpose, were prepared in two easy steps from the (S-) α-acetoxy acids **8a,b**[14] *via* the key intermediacy of the enantiopure α'-acetoxy-α-diazoketones **9a,b** as shown in **Scheme 4**.[13,15]

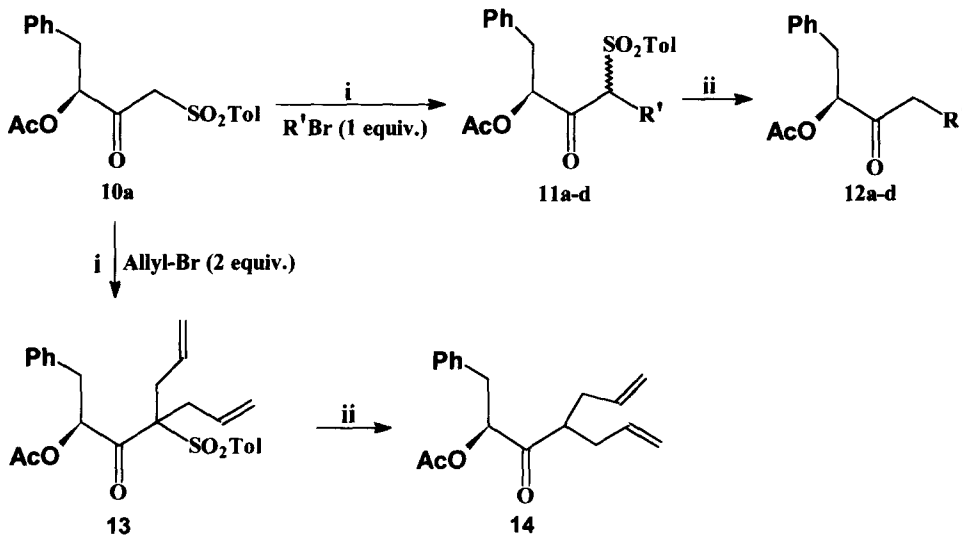


8a,b **9a,b** **10a,b**

a: **R** = Bn; **b**: R = i-Bu.

Scheme 4. i) $SOCl_2$, Bz, reflux; ii) excess CH_2N_2,ether,0°;
iii) 47% HBr, ether, 0°; iv) $NaSO_2Tol$, DMF, 25°.

α-Monoalkylation of the enantiopure γ-acetoxy-β-ketosulfone **10a** was initially taken up and carried out with one equivalent of the electrophile (R'Br) under the same conditions used in the γ-amino series (K_2CO_3 in DMF at RT) which produced the α-alkylated β-ketosulfones **11a-d** (57-76%) as mixtures of diastereomers. The latter upon desulfonation with Al(Hg) in refluxing THF-H_2O (9:1) gave the enantiopure α-acetoxy ketones **12a-d** in moderate to good overall yields. Under similar alkylation conditions, **10a** also underwent α,α-diallylation with two equivalents of allyl bromide to give **13** (95%) and the latter upon desulfonation then produced the α-acetoxy diallyl ketone **14** in high yield (**Scheme 5, Table 2**).

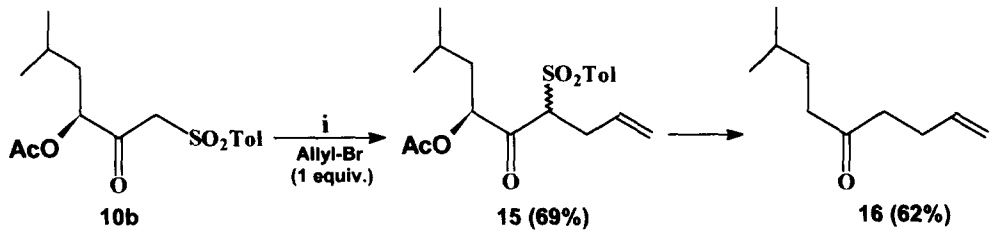


Scheme 5. i) K_2CO_3, DMF, RT; ii) Al(Hg), THF-H_2O (9:1), reflux.

Table 2. Synthesis of Enantiopure α-Acetoxy Ketones **12a-d** and **14** (**Scheme 5**).

Entry	R'	11,13 (yield%)	12,14 (yield%)
1	CH_2CH_3	**11a** (67)	**12a** (56)
2	$CH_2CH{=}CH_2$	**11b** (57)	**12b** (76)
3	CH_2CO_2Et	**11c** (67)	**12c** (75)
4	CH_2Ph	**11d** (76)	**12d** (80)
5	$CH_2CH{=}CH_2$	**13** (95)	**14** (86)

A limitation of this enantiopure α-acetoxy ketone synthesis was revealed when the above alkylation-desulfonation sequence was applied to the enantiopure γ-acetoxy-β-ketosulfone **10b**. Thus, α-monoalkylation of **10b** with allyl bromide gave **15** which upon desulfonation with Al(Hg) in refluxing aqueous THF, however, led to the over-reduced product **16** in 62% yield (**Scheme 6**). Under no conditions could this reduction be arrested at the desulfonation stage. Its worthy of note that such over-reduction problems were not encountered during desulfonation of the α-alkylated γ-amino-β-ketosulfones **4** and may be attributed to the poor nucleofugality of



Scheme 6. i) K_2CO_3, DMF, RT; ii) Al(Hg), THF-H_2O (9:1), reflux.

the carbamate group (in **4**) *vis-a-vis* the acetoxy function in **15**.

In summary, a facile new synthesis of enantiopure α-amino ketones has been developed from the chiral-pool derived γ-amino-β-ketosulfones *via* an α-alkylation-desulfonation sequence.[16] The methodology, by virtue of its operational simplicity and mild reaction conditions that allow alkylation reactions to be carried out with functionalized electrophiles, provides a versatile procedure for the synthesis of a wide variety of enantiopure α-amino ketones. Synthesis of enantiopure α-hydroxy ketones *via* α-alkylation-desulfonation of enantiopure γ-acetoxy-β-ketosulfones is, however, of limited scope.

EXPERIMENTAL

All melting points are uncorrected. IR Spectra were taken on a Perkin Elmer-297 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ (1% TMS) on JEOL FX-100 (100 MHz), Varian XL-200 (200 MHz) and XL-300 (300 MHz) instruments. Optical rotations were measured in $CHCl_3$ at 25° on a JASCO DIP-360 polarimeter. Enantiopure γ-amino-β-ketosulfones **3a-d**,[11,13] the (S)-α-acetoxy acids **8a,b**[14] and the γ-acetoxy-β-ketosulfones **10a,b**[13] were prepared according to literature procedures.

General Procedure for α-Alkylation and Subsequent Desulfonation of the γ-Amino- and γ-Acetoxy-β-ketosulfones (3,10) :

To a solution of **3** (or **10**) (0.112 mmol) and K_2CO_3 (0.015 g, 0.224 mmol) in DMF (2 ml), was added the respective alkylating agent R'X (0.112 mmol, for monoalkylation) at room temperature. After stirring for 5h, the reaction was neutralized with dil. HCl and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by chromatography over silica-gel (20-30% EtOAc in pet. ether) to give the monoalkylated sulfones **4** (or **11**) (**Table 1** & **2**). The latter were dissolved in 10% aqueous THF (5 ml) and freshly prepared Al(Hg) (0.022 g, 0.832 mmol) was added and the mixture heated under reflux for 2h. It was then filtered and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by chromatography over silica-gel (20-30% EtOAc in pet. ether) to give **5** (or **12**) (**Table 1** & **2**).

For α,α-dialkylation reactions (with **3b** and **10a**), the same procedure using 0.23 mmol of the alkylating agent was followed, finally affording after desulfonation, as above, the enantiopure ketones **7a,b** and **14**, respectively.

The following enantiopure α-amino ketones were prepared *via* the above representative procedure :

(*S*)-(7-Ethoxycarbonylamino-6-keto) octyl-2,2-dimethylpropionate (5a) : oil; $[\alpha]_D$ +6.80 (*c* , 1); IR (nujol): 3325, 1700 (br), 1520, 1120 cm^{-1}; δ_H : 1.19 (9H, s), 1.26 (3H, t, *J* 7), 1.34 (3H, d, *J* 9), 1.59-1.66 (6H, m), 2.51

(2H, m), 4.05 (2H, t, *J* 7), 4.11 (2H, q, *J* 7), 4.36 (1H, m), 5.40 (1H, br d). Found: C, 60.62 ; H, 9.12; N, 4.69; $C_{16}H_{29}O_5N$ requires C, 60.95; H, 9.21 and N, 4.44%.

(*S*)-6-Ethoxycarbonylamino-8-methylnon-1-en-5-one (5b) : oil; $[\alpha]_D$ +15.78 (c, 1.9); IR (nujol): 3325, 1730-1690 (br) cm^{-1}; δ_H : 0.92 (3H, d, *J* 6), 1.00 (3H, d, *J* 6), 1.25 (3H, t, *J* 7), 1.50-1.70 (3H, m), 2.30-2.80 (4H, m), 4.11 (2H, q, *J* 7), 4.44 (1H, dd, *J* 10, 6), 4.98-5.30 (3H, m), 5.50-6.11 (1H, m). Found: C, 64.68 ; H, 9.65; N, 5.46; $C_{13}H_{23}O_3N$ requires C, 64.73; H, 9.54 and N, 5.81%.

(*S*)-Ethyl (5-ethoxycarbonyl amino-4-keto-6-phenyl) hexanoate (5c) : oil; $[\alpha]_D$ +6.0 (c, 2.5); IR (nujol): 3340, 1736, 1690 cm^{-1}; δ_H: 1.21 (3H, t, *J* 7), 1.25 (3H, t, *J* 7), 1.95 (2H, t, *J* 6), 2.56 (1H, dd, *J* 7, *J* 6), 2.78 (1H, dd, *J* 10, *J* 6), 3.07 (2H, t, *J* 6), 4.08 (2H, q, *J* 7), 4.09 (2H, q, *J* 7), 4.44-4.80 (1H, m), 5.24 (1H, br d), 7.14-7.44 (5H, m). Found: C, 63.10; H, 7.41; N, 4.66; $C_{17}H_{23}O_5N$ requires C, 63.55; H, 7.17 and N, 4.36%.

(*S*)-6-Ethoxycarbonylamino-7-phenylhept-1-en-5-one (5d): oil; $[\alpha]_D$ +23.5 (c, 0.8); IR (CH_2Cl_2): 3410, 1730, 1690 cm^{-1}; δ_H: 1.19 (3H, t, *J* 7), 2.09-2.44 (2H, m), 2.56-3.18 (4H, m), 4.09 (2H, q, *J* 7), 4.71 (1H, m), 5.01 (1H, br d), 5.41-5.55 (2H, m), 5.65-5.89 (1H, m), 7.16-7.44 (5H, m). Found: C, 70.16; H, 7.29; N, 5.00; $C_{16}H_{21}O_3N$ requires C, 69.82; H, 7.64 and N, 5.09%.

(*S*)-1,5-Diphenyl-2-ethoxycarbonylaminopent-3-one (5e) : mp 109-111° (pet. ether-EtOAc); $[\alpha]_D$ +21.46 (c, 1.5); IR(nujol): 3320, 1710-1670 (br) cm^{-1}; δ_H: 1.19 (3H, t, *J* 7), 2.52-3.40 (6H, m), 4.09 (2H, q, *J* 7), 4.36-4.72 (1H, m), 5.2 (1H, br d), 6.8-7.8 (10H, m). Found: C, 72.97; H, 6.99; N, 4.28; $C_{20}H_{23}O_3N$ requires C, 73.85; H, 7.08 and N, 4.30%.

(*S*)-Ethyl (6-ethoxycarbonylamino-5-keto-7-phenyl) heptanoate (5f) : oil; $[\alpha]_D$ +15.2 (c, 1.0); IR(CH_2Cl_2): 3410, 1735, 1670 cm^{-1}; δ_H: 1.15-1.32 (6H, m), 1.70-2.00 (2H, m), 2.20-2.56 (4H, m), 3.03 (2H, dd, *J* 7, *J* 2), 4.11 (2H, q, *J* 7), 4.14 (2H, q, *J* 7), 4.48-4.68 (1H, m), 5.24 (1H, br d), 7.12-7.44 (5H, m). Found: C, 64.40; H, 7.31; N, 4.12; $C_{18}H_{25}O_5N$ requires C, 64.45; H, 7.46 and N, 4.18%.

(*S*)-4-Allyl-6-ethoxycarbonylamino-8-methylnon-1-en-5-one (7a) : oil; $[\alpha]_D$ +1.42 (c, 0.7); IR(CH_2Cl_2): 3410, 1730-1680 (br) cm^{-1}; δ_H: 0.93 (3H, d, *J* 5), 1.02 (3H, d, *J* 5), 1.25 (3H, t, *J* 7), 1.60-1.78 (3H, m), 2.20-2.57 (4H, m), 2.83 (1H, quintet, *J* 7), 4.13 (2H, q, *J* 7), 4.47 (1H, dd, *J* 10, *J* 4), 4.98-5.16 (5H, m), 5.53-5.98 (2H, m). Found: C, 68.31; H, 9.48; N, 4.75; $C_{16}H_{27}O_3N$ requires C, 68.33; H, 9.61 and N, 4.98%.

(S)-5-Ethoxycarbonylamino-3-ethyl-7-methyloct-4-one (7b) : oil; $[\alpha]_D$ +35.19 (c, 1.5); IR(CH_2Cl_2): 3410, 1720-1680 (br) cm^{-1}; δ_H: 0.75-1.01 (12H, m), 1.22 (3H, t, *J* 7), 1.35-1.89 (7H, m), 2.37-2.67 (1H, m), 4.09 (2H, q, *J* 7), 4.44 (1H, dd, *J* 10, *J* 4). Found: C, 65.28; H, 10.40; N, 5.10; $C_{14}H_{27}O_3N$ requires C, 65.37; H, 10.51; N, 5.45%.

The following enantiopure α-acetoxy ketones were prepared *via* the above representative procedure :

(*S*)-2-Acetoxy-1-phenylhex-3-one (12a) : oil; $[\alpha]_D$ +2.88 (c, 2.7); IR (nujol): 3020, 1730 (br), 1450 cm^{-1}; δ_H: 0.84 (3H, t, *J* 7), 1.36-1.76 (2H, m), 2.04 (3H, s), 2.20-2.60 (2H, m), 2.92 (1H, dd, *J* 8, *J* 14), 3.12 (1H, dd, *J* 5.5, *J* 14), 5.21 (1H, dd, *J* 5.5, *J* 14), 7.08-7.48 (5H, m). Found: C, 72.33; H, 7.50; $C_{14}H_{18}O_3$ requires C, 71.79 and H, 7.69%.

(*S*)-6-Acetoxy-7-phenylhept-1-en-5-one (12b) : oil; $[\alpha]_D$ +1.19 (c, 4.2); IR(nujol): 2920, 1745 (br), 1455 cm^{-1}; δ_H: 2.08 (3H, s), 2.20-2.60 (4H, m), 2.96 (1H, dd, *J* 8, *J* 15), 3.16 (1H, dd, *J* 6, *J* 15), 4.88-5.14 (2H, m), 5.26

(1H, dd, *J* 6, *J* 8), 5.56-6.00 (1H, m), 7.16-7.48 (5H, m). Found: C, 72.93; H, 7.45; $C_{15}H_{18}O_3$ requires C, 73.17 and H 7.32%.

(*S*)- Ethyl (5-Acetoxy-4-keto-6-phenyl) hexanoate (12c) : oil; $[\alpha]_D$ -2.73 (c, 4.1); IR(nujol): 2920, 1725 (br), 1450 cm^{-1}; δ_H: 1.28 (3H, t, *J* 7); 2.08 (3H, s), 2.44-2.84 (4H, m), 3.00 (1H, dd, *J* 8, *J* 15), 3.22 (1H, dd, *J* 5, *J* 15), 4.16 (2H, ABq, *J* 7, *J* 15), 5.30 (1H, dd, *J* 5, *J* 8), 7.16-7.56 (5H, m). Found: C, 66.05; H, 6.62; $C_{16}H_{20}O_5$ requires C, 65.75 and H, 6.85%.

(*S*)-2-Acetoxy-1,5-diphenylpent-3-one (12d) : oil; $[\alpha]_D$ -5.39 (c, 3.0); IR(nujol): 3025, 1725 (br), 1490 cm^{-1}; δ_H: 2.02 (3H, s); 2.40-3.20 (6H, m), 4.17 (1H, dd, *J* 6 *J*), 7.00-7.44 (10H, m). Found: C, 77.34; H, 6.50: $C_{19}H_{20}O_3$ requires C, 77.02 and H, 6.75%.

(*S*)-6-Acetoxy-4-allyl-7-phenylhept-1-en-5-one (14) : oil; $[\alpha]_D$ +13.42 (c, 1.2); IR(nujol): 2920, 1725 (br), 1440 cm^{-1}; δ_H: 2.04 (3H, s), 2.12-2.60 (4H, m), 2.72 (1H, m), 2.84 (1H, dd, *J* 8, *J* 15); 3.14 (1H, dd, *J* 4, *J* 15), 4.84-5.20 (4H, m), 5.36 (1H, dd, *J* 4, *J* 8), 5.48-5.92 (2H, m), 7.08-7.44 (5H, m). Found: C, 75.30; H, 7.88; $C_{18}H_{22}O_3$ requires C, 75.5 and H, 7.69%.

6-Acetoxy-8-methyl-4-tolylsulfonylnon-1-en-5-one (15, 1:1 mixture of 4*R*,6*S* and 4*S*,6*S* diastereoisomers) : oil; IR(nujol): 2930, 1740, 1710, 1625, 1600, 1490, 1430 cm^{-1}; δ_H: 0.90 (6H, m), 1.45-1.82 (3H, m), 2.18 (3H, s), 2.41 (3H, s), 2.50-2.68 (2H, m), 4.42 (0.5H, dd, *J* 4, *J* 8), 4.58 (0.5H, dd, *J* 4, *J* 8), 5.00-5.80 (4H, m), 7.40 (2H, d, *J* 8), 7.80 (2H, d, *J* 8).

8-Methylnon-1-en-5-one (16) : oil; IR (nujol) : 2930, 1710, 1600 cm^{-1}; δ_H: 0.88 (6H, m), 1.32-1.74 (3H, m), 2.30-2.40 (2H, m), 2.47-2.58 (4H, m), 4.82-5.60 (3H, m).

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