



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

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Received 6 March 1998; revised 27 May 1998; accepted 29 May 1998

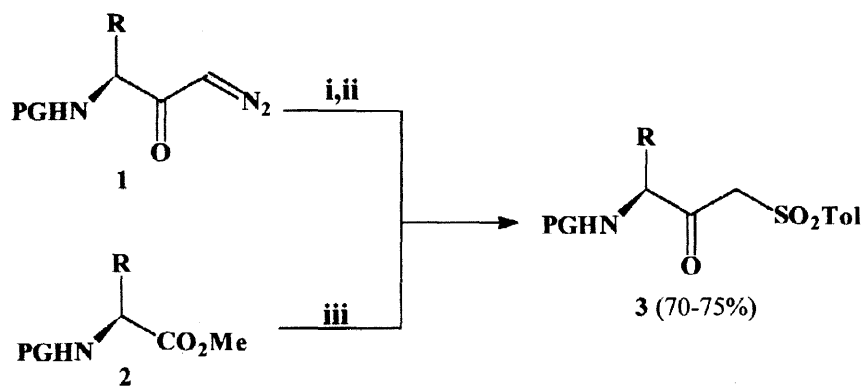
Abstract: Starting from 'chiral-pool' derived γ -amino- β -ketosulfones, a facile synthesis of enantiopure α -amino ketones has been developed *via* an α -alkylation-desulfonation sequence. Extension of this methodology to enantiopure α -acetoxy ketone synthesis, however, have met with limited success. © 1998 Elsevier Science Ltd. All rights reserved.

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 aldehydes² 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 ketone⁸ 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 -ketosulfones¹⁰ 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.*

γ -Amino- β -ketosulfones are a new class of chiral educts. The existing literature provided only one report by Lygo and Rudd¹¹ on the utility of chiral-pool derived γ -amino- β -ketosulfones in the synthesis of ethyldiene 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 NaSO₂Tol (DMF, RT)¹³ or via condensation¹¹ of excess α -lithio methyl tolyl sulfone with the amino acid esters **2a-c** (Scheme 1).

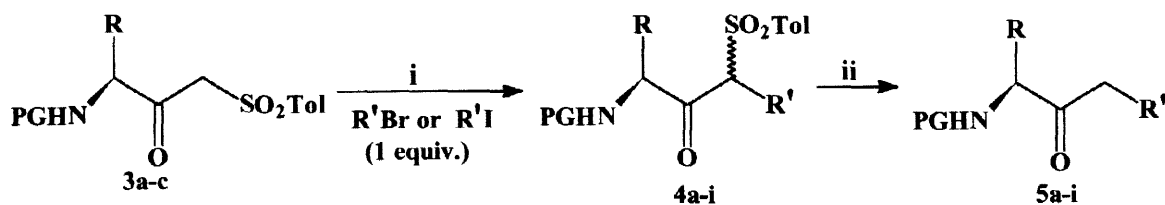


PG = CO₂Et

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

Scheme 1. i) 47% HBr, ether, 0°; ii) NaSO₂Tol, DMF, RT; iii) Li₂CHSO₂Tol, THF, -78°.

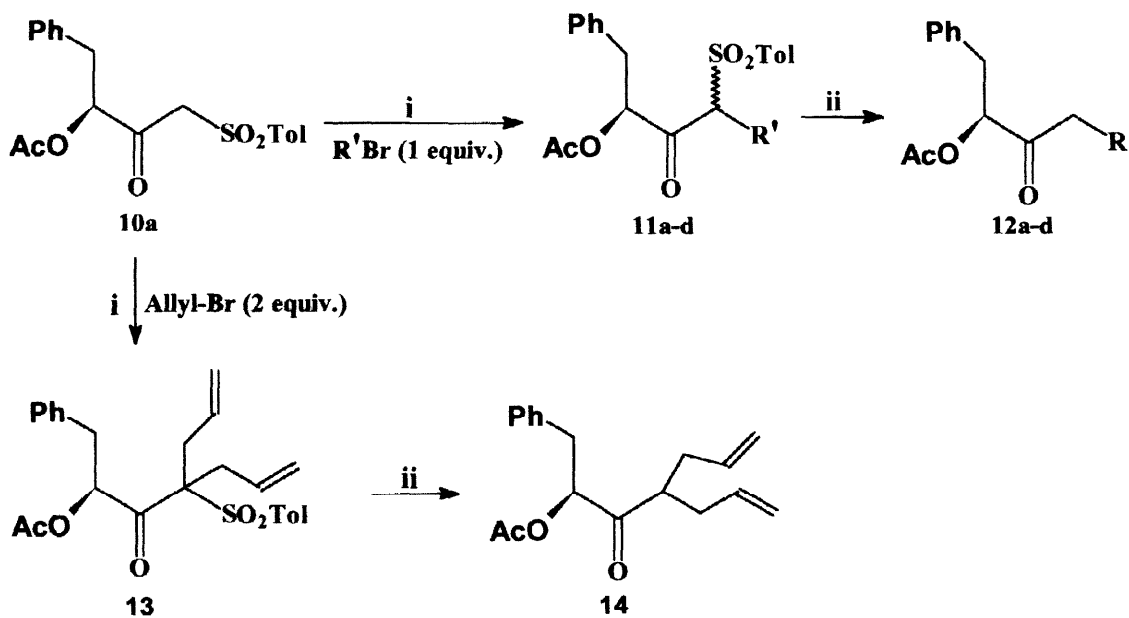
α -Alkylations of γ -amino- β -ketosulfones **3** were screened under a variety of conditions (NaH/DMF, NaH/DMSO, KOBu-*t*/THF, Triton-B/CH₂Cl₂-H₂O) which, however, gave incomplete conversions. Eventually, K₂CO₃ in DMF, the conditions described by Lygo in bromoester alkylation of such synthons,¹¹ produced the best results. Thus, reactions of **3a-c** with one equivalent of the electrophile (R' Br) in the presence of K₂CO₃ 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/NH₄Cl) 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 = CO₂Et

Scheme 2. i) K₂CO₃, DMF, RT; ii) Al(Hg), THF-H₂O (9:1), reflux.

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 -dialylation 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).

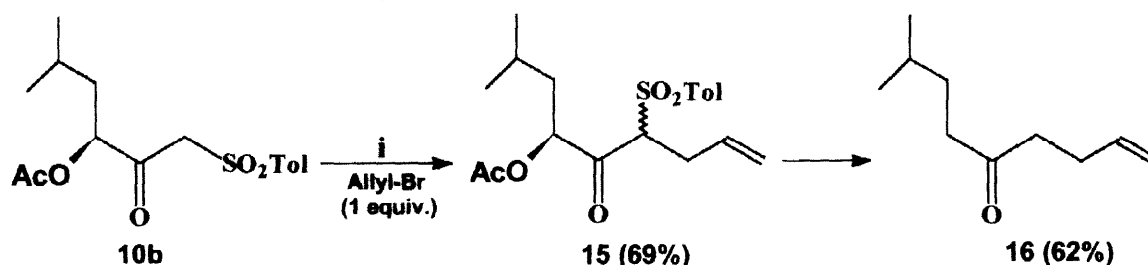


Scheme 5. i) K_2CO_3 , DMF, RT; ii) $Al(Hg)$, THF- H_2O (9:1), reflux.

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. ^1H 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 $\text{R}'\text{X}$ (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; C₁₆H₂₉O₅N requires C, 60.95; H, 9.21 and N, 4.44%.

(S)-6-Ethoxycarbonylamino-8-methylnon-1-en-5-one (5b) : oil; [α]_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; C₁₃H₂₃O₃N requires C, 64.73; H, 9.54 and N, 5.81%.

(S)-Ethyl (5-ethoxycarbonyl amino-4-keto-6-phenyl) hexanoate (5c) : oil; [α]_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; C₁₇H₂₃O₅N requires C, 63.55; H, 7.17 and N, 4.36%.

(S)-6-Ethoxycarbonylamino-7-phenylhept-1-en-5-one (5d): oil; [α]_D +23.5 (c, 0.8); IR (CH₂Cl₂): 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; C₁₆H₂₁O₃N requires C, 69.82; H, 7.64 and N, 5.09%.

(S)-1,5-Diphenyl-2-ethoxycarbonylamino-pent-3-one (5e) : mp 109-111° (pet. ether-EtOAc); [α]_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; C₂₀H₂₃O₃N requires C, 73.85; H, 7.08 and N, 4.30%.

(S)-Ethyl (6-ethoxycarbonylamino-5-keto-7-phenyl) heptanoate (5f) : oil; [α]_D +15.2 (c, 1.0); IR(CH₂Cl₂): 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; C₁₈H₂₅O₅N requires C, 64.45; H, 7.46 and N, 4.18%.

(S)-4-Allyl-6-ethoxycarbonylamino-8-methylnon-1-en-5-one (7a) : oil; [α]_D +1.42 (c, 0.7); IR(CH₂Cl₂): 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; C₁₆H₂₇O₃N requires C, 68.33; H, 9.61 and N, 4.98%.

(S)-5-Ethoxycarbonylamino-3-ethyl-7-methyloct-4-one (7b) : oil; [α]_D +35.19 (c, 1.5); IR(CH₂Cl₂): 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; C₁₄H₂₇O₃N 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; [α]_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; C₁₄H₁₈O₃ requires C, 71.79 and H, 7.69%.

(S)-6-Acetoxy-7-phenylhept-1-en-5-one (12b) : oil; [α]_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; C₁₅H₁₈O₃ requires C, 73.17 and H 7.32%.

(S)- Ethyl (5-Acetoxy-4-keto-6-phenyl) hexanoate (12c) : oil; [α]_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; C₁₆H₂₀O₅ requires C, 65.75 and H, 6.85%.

(S)-2-Acetoxy-1,5-diphenylpent-3-one (12d) : oil; [α]_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; C₁₉H₂₀O₃ requires C, 77.02 and H, 6.75%.

(S)-6-Acetoxy-4-allyl-7-phenylhept-1-en-5-one (14) : oil; [α]_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; C₁₈H₂₂O₃ 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).

Acknowledgements:

Financial supports from CSIR (01/1371/95/EMR-II) and Jadavpur University (Senior Research Fellowships to D. S. S. and S. M.) are gratefully acknowledged.

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16. The *L*-proline derived enantiopure γ -amino- β -ketosulfone *via* a similar α -alkylation - desulfonation sequence also led to a wide variety of functionalized α -prolinyl ketones, details of which would be published separately.