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An Approach to Homochiral Fused and Spiro Cyclopentenones

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Abstract: An asymmetric approach to the Ni(CO)₄ induced alkyne-allyl halide cyclizationcarbonylation process by the use of homochiral acetylenic sulfoxides to afford enantiopure [5+8] fused and spiro cyclopentenones is reported.

During the last years we have been working on the synthesis of cyclopentenones by means of the Ni(CO)₄ induced carbonylative inter and intramolecular cyclization of acetylenes with allyl halides.¹ By proper choice of the substrates, bicyclic fused and spiro cyclopentenones can be obtained in a single synthetic operation with total regio and diastereoselectivity.² As an extension of our efforts in this field we wish to report on the development of an asymmetric approach to this process making use of homochiral acetylenic sulfoxides as chiral auxiliaries to obtain enantiopure [5+8] fused and spiro systems (Scheme 1).



a: R=CH₃; b: R=*n*-Bu (i): Ni(CO)₄, MeOH, KOAc, r.t.; (ii): 1) chromatography; 2) MCPBA, CH₂Cl₂, rt; (iii): Al-Hg, THF-H₂O (10%)

SCHEME 1

The use of sulfoxides as chiral auxiliaries is well precedented in the literature, although their applications to transition metal promoted reactions are scarce.³ In our case, a chiral sulfoxide group adjacent to the more electronegative carbon atom of the acetylenic triple bond may be expected to exert both a strong regiodirecting effect and an efficient diastereocontrol on the new stereogenic centers arising from the insertion steps leading to the final cycloadducts.¹

In order to explore the diastereoselection induced by the sulfoxide moiety, initial studies were carried out with (\pm) -**1a** and 3-bromocyclooctene **2** in the presence of Ni(CO)₄ under our previously developed standard conditions^{2,4,5} (see Table, entry 1). Thus, although cycloadduct **4a** was obtained in moderate yield (28%), it corresponded to a mixture of only the two *trans*-fused S-epimers in a high diastereomeric ratio (82:18) as deduced from ¹H NMR data.⁶ Addition of one equivalent of KOAc⁷ with respect to the starting halide afforded a substantially higher yield (63%) of the desired cycloadducts, with no improvement in the diastereomeric ratio (entry 2).

Table. Ni(CO)4 promoted cyclization of allyl halides with acetylenic sulfoxides entry acetylene **R** allyl halide Additive (equiv)⁴ Cycloadduct, Yield % (d.r.)^b

entry	acotylene		unyi nunuc	Hudditive (equit)	Cycloudduct, Alcid / (d.i.)
1	(±)-1a	CH ₃	2		4a , 28 (82:18)
2	(±)- 1a	CH ₃	2	KOAc (1)	4a , 63 (82:18)
3	(+)-1b	Bu	2	KOAc (1)	4b, 44 (82:18)
4	(±)-1a	CH ₃	3		5a, 16 ^c ; 6a, 19; 8a, 9
5	(±)-1a	CH ₃	3	KOAc (1)	7a, 43; 8a, 17
6	(±)- 1a	CH ₃	3	KOAc (0.5)	5a , 31 ^c , 6a , 14; 8a , 17
7	(+)-1b	Bu	3	KOAc (0.5)	5b , 21 ^c ; 6b , 9

a. Referred to allyl halide; b. Diastereomeric ratio as deduced from ¹HNMR data; c. A single diastereomer by ¹HNMR



As expected from the high polarization of the acetylene, only one of the two possible regioisomers resulting from acetylene insertion was observed.⁴ From the epimeric mixture **4a**, the major isomer was isolated by flash chromatography and the relative configuration of the stereogenic centers was established by X-ray diffraction analysis to be rel(SR, 3aR, 4R, 9aR).⁸ Since initial attempts to direct reductive cleavage of the sulfinyl cyclopentenones were unsuccessful, removal of the aryl sulfoxide moiety was carried out by a two-step sequence: oxidation to the vinyl sulfone (±)-**9a** (MCPBA, CH₂Cl₂, rt.) followed by reductive cleavage to (±)-**10a** (Al-Hg, THF-H₂O)¹⁰ in 94% overall yield.

Similarly, starting from homochiral sulfoxide $S(+)-1b^9$ (entry 3), isolation of the major diastereomer of the epimeric mixture 4b, and further removal of the chiral auxiliary by the above two step sequence, afforded fused [5+8] cyclopentenone (-)-10b¹¹ in 30% overall yield. The homochiral nature of (-)-10b was confirmed by ¹HNMR in the presence of the chiral lanthanide shift reagent Eu(hfc)₃ and comparison of the C(1)H signals with that of racemic (\pm)-10b.¹² Since only one set of signals was observed, this result confirms the stereogenic integrity of the sulfoxide moiety in the Ni(0) promoted process. Based on the

X-ray diffraction analysis of the major diastereomer of the epimeric mixture 4a (see above), the absolute configuration of (-)-4b (major isomer) and, hence, that of (+)-9b and (-)-10b could be inferred, as indicated in Scheme 2. On the other hand, the absolute configuration of (-)-10b was independently assigned by the negative Cotton effect observed in the circular dicroism spectrum,¹¹ a result in agreement with the sign predicted by the octant rule for the MMX minimized structure.¹³

This methodology has also been applied to the synthesis of homochiral spiro [5+8] systems starting from allyl halide 3. In this case, product distribution was complicated by the competition of two alternative cyclization modes leading to cyclopentenones 5 or phenolic adducts 6.1^4 Reaction with (\pm)-1a under standard conditions (entry 4) led to (\pm)-5a and (\pm)-6a in nearly equimolar amounts. Concerning diastereoselectivity, only one single spirocycloadduct 5a was obtained.¹⁵ The stereochemistry of the carbon stereogenic centeres 5 and 6 was inferred from mechanistic considerations² and independently confirmed by a single crystal X-ray diffraction analysis of (\pm)-5a to be rel(SR, 5S, 6S).⁸

In this series, KOAc was crucial for the control of the product distribution and overall yields (entries 5 and 6).⁷ Starting from homochiral acetylenic sulfoxide S(+)-1b, a single cycloadduct (-)-5b was obtained in moderate yield (entry 7). Removal of the sulfoxide chiral auxiliary by oxidation to (+)-11b and reductive cleavage (see above), afforded homochiral [5+8] spiroadduct (+)-12b^{16,17} in 20% overall yield from the easily available S(+)-1b and allyl halide 3. As in the fused series, based on X-ray diffraction analysis of (±)-5a, the absolute configurations of (-)-5b, (+)-11b, and (+)-12b could be determined¹⁸ (Scheme 2).



Further work concerning the applicability of this methodology to the synthesis of related homochiral fused and spiro cyclopentenones is currently under way in our laboratory.

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References and Notes

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- 2 Pagès, L.; Llebaria, A.; Camps, F.; Molins, E.; Miravitlles, C.; Moretó, J. M. J. Am. Chem. Soc. 1992, 114, 10449-10461. In this process, ring closure and the nearby carbonylation are syn.
- 3 a) For general reviews of sulfoxides as chiral auxiliaries see: Posner, G.H., in The Chemistry of Sulfones and Sulfoxides, eds. S. Patai, Z. Rappoport, and C.J.M. Stirling, Wiley, New York, 1988, pp. 828-850; Walker, A.J. Tetrahedron: Asymmetry, 1992, 3, 961-998; b) For applications to transition metal promoted reactions, see: Griffiths, S.L.; Marcos, C.F.; Perrio, S.; Saberi, S.P.; Thomas, S.E.; Tustin, G.J.; Wierzchleyski, A.T. Pure Appl. Chem. 1994, 66, 1565-1572; Hiroi, K.; Arinaga, Y. Tettrahedron Lett. 1994, 35, 153-156; Paley, R.S.; de Dios, A.; Fernández de la Pradilla, R. Tetrahedron Lett. 1993, 34, 2429-2432.
- 4 Camps, F.; Coll, J.; Moretó, J. M.; Torras, J. J. Org. Chem. 1989, 54, 1969-1978.
- 5 CAUTION !: Tetracarbonylnickel is an extremely toxic, volatile compound and special precautions have to be taken in its use.
- 6 The trans- stereochemistry of the ring fusion in 4a as well as the mutual cis- arrangement of H_{3a} and H₄ (see Scheme 2 for numbering) were first assigned by comparison of the ¹HNMR chemical shifts and coupling constants with those already reported by us for other fused [5+8] cycloadducts,² and later confirmed by X-ray diffraction analysis (this work).
- 7 Although the precise role played by acetate ion remains still obscure, the strong dependence of the product distribution on its concentration seems to entail its active involvement in one or more steps of the mechanistic pathway.
- 8 A list of refined coordinates have been deposited by the Editor at the Cambridge Crystallographic Data Centre. Any request should be accompannied by a full literature citation for this paper. Please note that the crystallographic numbering differs from that used in this communication.
- 9 Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. J. Org. Chem. 1987, 52, 1078-1082.
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- Compound (-)-10b: Rf 0.56 (silica gel, hexane/EtOAc 8:2); IR (neat): 2950, 1733, 1704; CD: $[\theta]_{255} = -522 \ (\pi \rightarrow \pi^*)$, 11 $[0]_{310} = -1250 \text{ (n} \rightarrow \pi^*), (c \ 0.092, \text{ CHCl}_3, 22^{\circ}\text{C}); [a]_D - 7.9 (c \ 0.56, \text{ CHCl}_3, 22^{\circ}\text{C}); ¹H NMR (CDCl}_3, 200 \text{ MHz}): 0.87$ (m, 3H, J=6.8 Hz, CH3), 0.90-2.29 (m, 16H), 2.86-3.00 (m, 1H), 3.16-3.32 (m, 1H), 3.54 (s, 3H, CH3), 7.05 (broad s, 1H); 13C NMR (CDC13, 50 MHz): 13.8 (CH3), 22.4 (CH2), 24.4 (CH2), 24.8 (CH2), 25.0 (CH2), 26.5 (CH2), 27.2 (CH₂), 29.7 (CH₂), 34.9 (CH₂), 42.2 (CH), 43.8 (CH), 51.4 (CH), 52.7 (CH₃), 144.0 (C), 160.4 (CH), 174.5 (C), 210.2 (C=O); Elemental analysis: Calcd for C17H26O3, C, 73.35%, H, 9.41%; Found, C, 73.34%, H, 9.44%.
- 12 Racemic (±)-10b was obtained in 80% yield by the Ni(CO)4 promoted reaction of 1-hexyne with 3-bromocyclooctene (2) in the presence of 2 equivalents of KOAc under the conditions described in ref.2
- 13 PCMODEL, Serena Software, Bloomington, IN
- 14 In addition, monocyclic adducts 7a, resulting from acetylene insertion on the π -allylnickel intermediate followed by carbonylation and methanolysis, and 8a, arising from a Michael-type reaction between the acetylene and a σ-allylnickel species were also isolated in some cases (see Table).
- 15 Since complex crude mixtures were obtained, it is not possible to exclude other minor diastereomers, not isolable by the conventional purification techniques.
- Only one set of signals was observed by ¹HNMR in the presence of the chiral shift reagent Eu(hfc)₃. 16
- 17 Compound (+)-12b: Rf 0.41 (silica gel, hexane/EtOAc 9:1); IR (neat): 2925, 1737, 1701; CD: $[\theta]_{330} = -550 (n \rightarrow \pi^*)$ (c 0.040, CHCl₃, 22°C); [a]D +46.1 (c 1.0, CHCl₃, 22°C); ¹H NMR (CDCl₃, 200 MHz): 0.88 (t, 3H, J=7 Hz, CH₃), 1.20-2.60 (m, 20 H), 2.88 (dd, 1H, J=7.8 Hz, J'=2.0 Hz), 3.52 (s, 3H, CH₃), 7.00 (broad s, 1H, CH); ¹³C NMR (CDCl3, 50 MHz): 13.9 (CH3), 22.5 (CH2), 24.0 (CH2), 24.7 (CH2), 25.4 (CH2), 26.2 (CH2), 28.0 (CH2), 28.2 (CH₂), 30.0 (CH₂), 33.7 (CH₂), 40.9 (CH₂), 48.9 (CH), 50.0 (C), 51.6 (CH₃), 145.2 (C), 151.9 (CH), 175.6 (C), 212.1 (C=O); Elemental analysis: Calcd for C18H28O3, C, 73.93%, H, 9.65%; Found, C, 74.03%, H, 9.71%.
- The absolute configuration of (+)-12b was also assigned independently by circular dicroism. The observed negative 18 Cotton effect is in agreement with the absolute configuration shown in Scheme 2.

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