Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 3, pp. 665-668, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00055-0

An Approach to Homochiral Fused and Spiro Cyclopentenones

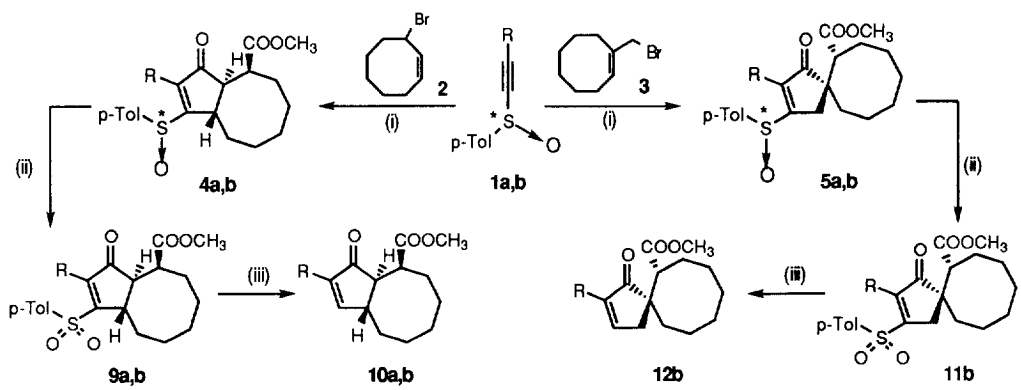
Juan Manuel Villar, Antonio Delgado,¶ Amadeu Llebaria, and Josep M. Moretó*

Departament de Química Orgànica Biològica, C.I.D. (C.S.I.C.), Jordi Girona 18-26, 08034 Barcelona.

¶Universitat de Barcelona, Facultat de Farmàcia, Laboratori de Química Farmacèutica, Avgda. Joan XXIII, s/n, 08028 Barcelona, Spain.

Abstract: An asymmetric approach to the $Ni(CO)_4$ induced alkyne-allyl halide cyclization-carbonylation 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=CH_3; **b**: R=*n*-Bu

(i): $Ni(CO)_4$, MeOH, KOAc, r.t.; (ii): 1) chromatography; 2) MCPBA, CH_2Cl_2, rt; (iii): Al-Hg, THF-H_2O (10%)

SCHEME 1

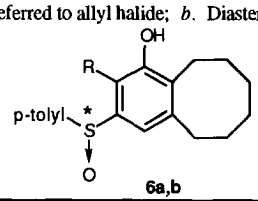
The use of sulfoxides as chiral auxiliaries is well precedented in the literature, although their applications to transition metal promoted reactions are scarce.[3] In our case, a chiral sulfoxide group adjacent to the more electronegative carbon atom of the acetylenic triple bond may be expected to 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 (±)-**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 KOAc[7] 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).

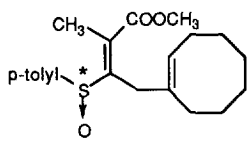
Table. $Ni(CO)_4$ promoted cyclization of allyl halides with acetylenic sulfoxides

entry	acetylene	R	allyl halide	Additive (equiv)[a]	Cycloadduct, Yield % (d.r.)[b]
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

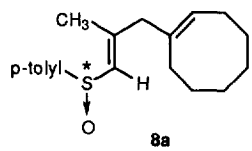
a. Referred to allyl halide; *b*. Diastereomeric ratio as deduced from ^{1}HNMR data; *c*. A single diastereomer by ^{1}HNMR



6a,b



7a



8a

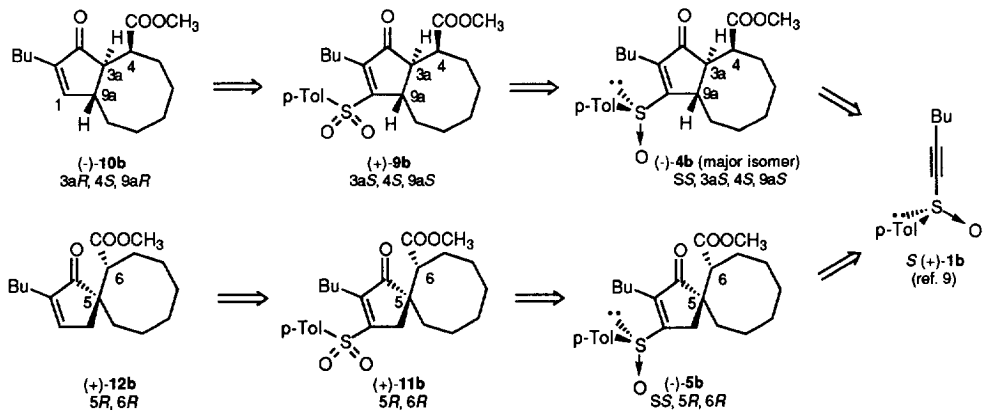
As expected from the high polarization of the acetylene, only one of the two possible regioisomers resulting from acetylene insertion was observed.[4] From the epimeric mixture **4a**, the major isomer was isolated by flash chromatography and the relative configuration of the stereogenic centers was established by X-ray diffraction analysis to be *rel*(*SR*, 3a*R*, 4*R*, 9a*R*).[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, CH_2Cl_2, rt.) followed by reductive cleavage to (±)-**10a** (Al-Hg, THF-H_2O)[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 (-)-**10b**[11] in 30% overall yield. The homochiral nature of (-)-**10b** was confirmed by ^{1}HNMR in the presence of the chiral lanthanide shift reagent Eu(hfc)$_3$ and comparison of the C(1)H signals with that of racemic (±)-**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 difraction 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**.[14] Reaction with (±)-**1a** under standard conditions (entry 4) led to (±)-**5a** and (±)-**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 considerations[2] and independently confirmed by a single crystal X-ray diffraction analysis of (±)-**5a** to be *rel*(*SR*, 5*S*, 6*S*).[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 determined[18] (Scheme 2).



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.

Acknowledgements: Financial support from DGICYT (Project PB 91-0612-C03-03) is gratefully acknowledged. J.M.V. thanks CIRIT (Generalitat de Catalunya) for a predoctoral fellowship.

References and Notes

1 Llebaria, A.; Moretó, J. M. *J. Organomet. Chem.* **1993**, *451*, 1-13.

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. *Tetrahedron 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 H_4 (see Scheme 2 for numbering) were first assigned by comparison of the ^{1}HNMR 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.

10 Ellingsen, P. O.; Undheim, K. *Acta Chem. Scand. B* **1979**, *33*, 528-530.

11 Compound (-)-**10b**: R_f 0.56 (silica gel, hexane/EtOAc 8:2); IR (neat): 2950, 1733, 1704; CD: $[\theta]_{255}$ = -522 ($\pi\rightarrow\pi^*$), $[\theta]_{310}$ = -1250 ($n\rightarrow\pi^*$), (c 0.092, $CHCl_3$, 22ºC); $[\alpha]_D$ -7.9 (c 0.56, $CHCl_3$, 22ºC); ^{1}H NMR ($CDCl_3$, 200 MHz): 0.87 (m, 3H, J=6.8 Hz, CH_3), 0.90-2.29 (m, 16H), 2.86-3.00 (m, 1H), 3.16-3.32 (m, 1H), 3.54 (s, 3H, CH_3), 7.05 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): 13.8 (CH_3), 22.4 (CH_2), 24.4 (CH_2), 24.8 (CH_2), 25.0 (CH_2), 26.5 (CH_2), 27.2 (CH_2), 29.7 (CH_2), 34.9 (CH_2), 42.2 (CH), 43.8 (CH), 51.4 (CH), 52.7 (CH_3), 144.0 (C), 160.4 (CH), 174.5 (C), 210.2 (C=O); Elemental analysis: Calcd for $C_{17}H_{26}O_3$, 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.

16 Only one set of signals was observed by ^{1}HNMR in the presence of the chiral shift reagent Eu(hfc)$_3$.

17 Compound (+)-**12b**: R_f 0.41 (silica gel, hexane/EtOAc 9:1); IR (neat): 2925, 1737, 1701; CD:$[\theta]_{330}$ = -550 ($n\rightarrow\pi^*$) (c 0.040, $CHCl_3$, 22ºC); $[\alpha]_D$ +46.1 (c 1.0, $CHCl_3$, 22ºC); ^{1}H NMR ($CDCl_3$, 200 MHz): 0.88 (t, 3H, J=7 Hz, CH_3), 1.20-2.60 (m, 20 H), 2.88 (dd, 1H, J=7.8 Hz, J'=2.0 Hz), 3.52 (s, 3H, CH_3), 7.00 (broad s, 1H, CH); ^{13}C NMR ($CDCl_3$, 50 MHz): 13.9 (CH_3), 22.5 (CH_2), 24.0 (CH_2), 24.7 (CH_2), 25.4 (CH_2), 26.2 (CH_2), 28.0 (CH_2), 28.2 (CH_2), 30.0 (CH_2), 33.7 (CH_2), 40.9 (CH_2), 48.9 (CH), 50.0 (C), 51.6 (CH_3), 145.2 (C), 151.9 (CH), 175.6 (C), 212.1 (C=O); Elemental analysis: Calcd for $C_{18}H_{28}O_3$, C, 73.93%, H, 9.65%; Found, C, 74.03%, H, 9.71%.

18 The absolute configuration of (+)-**12b** was also assigned independently by circular dicroism. The observed negative Cotton effect is in agreement with the absolute configuration shown in Scheme 2.

(*Received in UK* 9 *January* 1995)