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The stereocontrolled synthesis of polyfunctional organosulfur compounds via chiral azetidinium salts and epoxyamines

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Dedicated to Professor Jan Michalski on the occasion of his 85th birthday

Abstract—The stereocontrolled synthesis of functionalized organosulfur compounds of a general formula: $Bn_2NCH(CH_3)CH(OH)CH_2SX$ [where: $X = SO_3Na$ or $SP(S)(OR)_2$] was achieved by a regioselective opening of enantiomerically >98% pure (2*S*,3*R*)- and (2*S*,3*S*)-*N*,*N*-dibenzyl-2-hydroxy-3-methylazetidinium bromides and/or (1*R*)-[1′(*S*)-dibenzylamino)ethyl]oxiranes with thiosulfate and dithiophosphate anions. The attack of both nucleophiles was directed exclusively at the less substituted carbon atom of the heterocyclic ring.

1. Introduction

Over the last 25 years the development of new and efficient chiral ligands for catalytic asymmetric synthesis has been one of the most challenging subjects of organic synthesis.[1] Over recent years there has been growing interest in sulfur containing ligands.[2] According to the literature[3] the different electronic properties of sulfur compared to oxygen as the chelating atom and the fact that sulfur can become chiral when coordinated to a metal establishes an advantage of these type of ligands. Utilization of nitrogen and sulfur as chelating atoms in ligands have afforded moderate to excellent results in allylic alkylation,[4] hydrogenation,[3,5] diethylzinc addition,[6] conjugate addition to enones[2,7] and metal catalyzed cross–coupling.[2]

We have reported, previously, the preparation of a variety of polyfunctional heteroatom containing organic compounds bearing amino and hydroxy functional moieties from 3-hydroxyazetidinium salts and amino epoxides.[8]

Both Barluenga et al.[9] and Concellón et al.[10] have developed elegant methods of the synthesis of chiral hydroxyazetidinium salts and amino oxiranes of high enantiomeric purity, and we realized that our strategy might be applicable for the synthesis of optically active polyfunctional building blocks and/or potential chiral ligands.

We report, herein, the application of a regioselective ring opening of optically active azetidinium salts **1** and **2** and oxirane **3** at the less substituted carbon atom with sulfur nucleophiles for the stereocontrolled synthesis of three functional compounds with the butane skeleton.

2. Results and discussion

Starting materials: the optically active (2*S*,3*R*)- and (2*S*,3*S*)-*N*,*N*-dibenzyl-3-hydroxy-2-methylazetidinium bromides **1** and **2** as well as (1*R*)-[1′(*S*)-(dibenzylamino) ethyl] oxirane **3** were prepared, respectively, from *N*,*N*-dibenzylalaninal and the methyl ester of *N*,*N*-dibenzylalanine, according to the procedures described by Barluenga et al.[9] and Concellón et al.[10] The method used the manipulation of these two starting materials with non-chelation control during the generation of the second stereogenic centre in order to obtain, from

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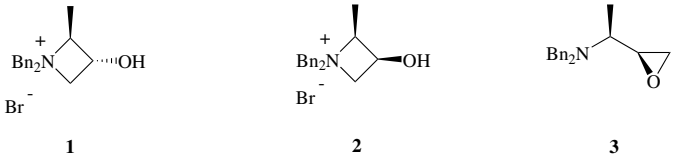
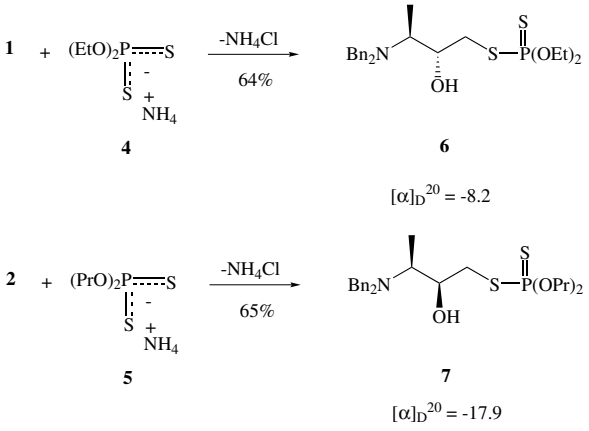


Figure 1.

L-alanine, the two diastereomeric salts **1** and **2** and oxirane **3** (Fig. 1).

We prepared the enantiomerically pure starting material **3** with the spectroscopic data in accordance with those described.[9,10] 3-Hydroxyazetidinium salts **1** and **2** were, however, obtained as bromides and their spectra performed in CD_3OD while in the literature only the spectra of (2*S*,3*R*)-*N*,*N*-dibenzyl-3-hydroxy-2-methylazetidinium tetrafluoroborate were given in DMSO-d_6.[10] The spectral data and diastereomeric purity of **1** and **2** have been reported.[11]

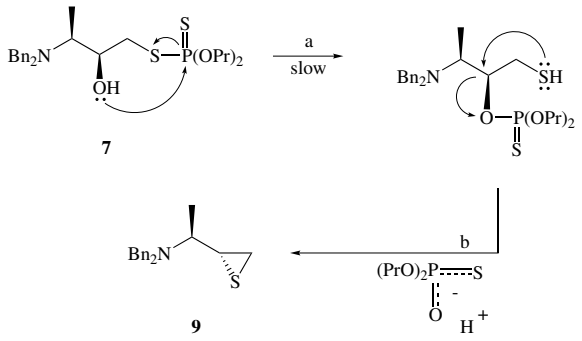
Treatment of azetidinium salts **1** and **2** with anions of *O*,*O*-dialkyl dithiophosphoric acids under the conditions applied earlier for achiral compounds[8e] (the room temperature, DMF as solvent, 24 h) involved the nucleophilic opening of the azetidinium ring, resulting in the formation of the corresponding *O*,*O*-dialkyl,-*S*-3-*N*,*N*-dibenzylamino-(2-hydroxy)butyl dithiophosphates (Scheme 1).[12]



Scheme 1.

It is well known[13] that compounds of structure **6** and **7** undergo secondary reactions via transphosphorylation, followed by the leaving of dialkyl thiophosphoric acid from *O*-phosphorylated intermediate product to afford thiirane **9** as a final product (Scheme 2).

It was demonstrated in our previous paper[8e] that the rate of secondary reactions (a) and (b) depends strongly on the structure of *S*-aminohydroxyalkyl dithiophosphate, particulary on the properties of substituents at the nitrogen and at the phosphorus atoms. Fortunately, dithiophosphates **6** and **7** are stable enough to be purified via column chromatography and were fully characterized.[14]

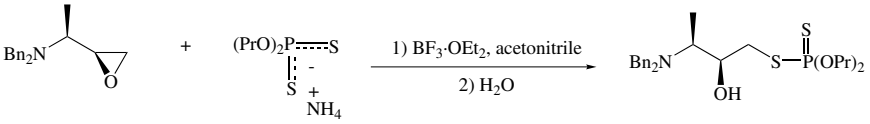


Scheme 2.

The presence of the single peaks in the ^{31}P NMR spectra of diastereomers **6** and **7** and the character of their ^{1}H, ^{13}C and HMQC spectra showed that the attack of nucleophilic reagents **4** or **5** took place exclusively at the non-stereogenic (less substituted) carbon atom C-4. Thus the synthetic procedure does not affect the stereochemistry of any of the stereogenic centres. Any epimerization occuring at the stage of the synthesis or the purification would lead to the formation of the second diastereoisomer, easily detectable in the reaction mixture. The circumstance that the free hydroxy group in **1** or **2** does not disturb the reaction course is probably due to the reaction conditions. It is not obvious in the reaction of 3-hydroxyazetidinium salts with other nucleophiles.[8a–c]

A similar reaction course, as for azetidinium salts **1** and **2** was observed for amino oxirane **3**, reacting with *O*,*O*-dipropyl dithiophosphate anion **5** (Scheme 3). The reaction was carried out in the presence of $Et_2O{\cdot}BF_3$ to avoid the formation of thiirane **9**, which was expected to be the favoured product of the reaction of **3** with **5**.[15]

Dithiophosphate **7** (62%), obtained according to Scheme 3 exhibited the same spectral data as that synthesized from azetidinium salts **2**, as well as the same chemical yield and enantiomeric purity. This means that oxirane **3** was attacked by the nucleophilic reagent at the less substituted (non-stereogenic) carbon atom. We did not observe any essential differences in the reaction results when we used both types of starting materials, **2** or **3**, for the synthesis of **7**. The only aim of the investigation of the two substrates **2** and **3** was to learn whether the nucleophilic ring opening of the both heterocycles would be regioselective enough to synthesize **7** as one product and in its diastereomerically pure form. The knowledge about the chemistry of azetidinium salts[16] and oxiranes[17] would not give such certainty. Furthermore, our results should not be generalized. Taking into



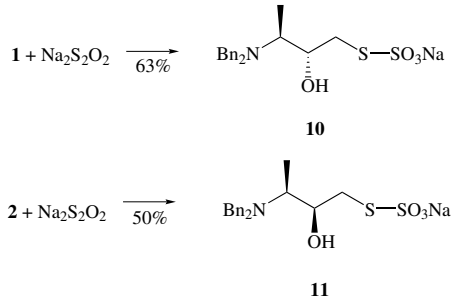
3 5 7

Scheme 3.

account an easier accessibility of oxirane **3** versus salt **2**, the former is the substrate of choice.

While this work was being realized, new results concerning the reaction of epoxides with phosphoroorganic dithio acids were reported.[18] Oxiranes, which were subjected to the reaction bore in their structure only alkyl, aryl or alkoxyl substituents. Therefore, we decided to test under the reported conditions (0 °C, toluene) our substrate, oxirane **3**. As a result of the reaction of **3** with an equimolar amount of *O*,*O*-diethyl hydrogen dithiophosphate only one product was found by ^{31}P NMR spectroscopy: dithiophosphate **7′** δ 96.28 ppm (100%). Although ^{1}H and ^{13}C NMR spectroscopy confirmed the structure of the product, a minute amount of impurity derived probably from the substrate **3** was also visible. The authors of the above mentioned[18] paper have described, (without experimental details) the reduction of *S*-2-hydroxyalkyl dithiophosphates into the corresponding hydroxy thiols. Our attempts to transform the crude dithiophosphate **7′** into the thiol with $LiAlH_4$ unfortunately failed.

The other sulfur nucleophile, which was found to react with 3-hydroxyazetidinium salts forming the C–S bond was sodium thiosulfate (Scheme 4).



Scheme 4.

The reaction was carried out at room temperature in water within 24 h. The reaction products **10** and **11** did not require purification.[19] With such compounds being pseudohalogens they are also potential starting materials for the synthesis of the corresponding 3-amino-2-hydroxybutanethiols via the reduction or hydrolysis reaction. The observation that the formation of thiosufonates is often accompanied by a minute amount of the corresponding disufide shows the pseudohalogenic character of these compounds.[8d] Attempts to transform thiosulfonates under hydrolytic and/or reductive conditions into amino hydroxy thiols are currently underway.

3. Conclusion

In conclusion, a stereocontrolled synthesis of functionalized with amino and hydroxy groups organosulfur compounds has been accomplished starting from the enantiomerically pure (2*S*,3*S*)- and (2*S*,3*R*)-*N*,*N*-dibenzylamino-3-hydroxy-2-methylazetidinium bromides and (1*R*)-[1′(*S*)-dibenzylamino)ethyl] oxirane. Regioselective opening of azetidinium and oxirane rings at the less substituted carbon with sulfur S^{II} nucleophiles allowed us to prepare useful precursors of tridentate ligands and building blocks of the determined configuration and enantiomeric purity.

Acknowledgements

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11. *Starting materials*: Spanish authors have described several versions of the synthesis of aminohalohydrins[9,10]-precursors of compounds **1**–**3**. The method, we used[9b] gave oxirane **3** of de >90% (ee >99%) as a crude product; after purification by column chromatography (silica gel), oxirane **3** was described as pure *threo*. Our samples were of the same purity.

(2*S*,3*R*)-1,1-Dibenzyl-3-hydroxy-2-methylazetidinium bromide 1 was obtained from the corresponding bromohydrin[9b] of de >93% and after the crystallization was pure (de >99%). Yield: 55% (pale yellow solid). $[\alpha]_D^{20} = +20.5$ (*c* 4.0, MeOH). Lit.[6] gives $[\alpha]_D^{20} = +16$ (*c* 1, acetone). IR (KBr): ν_{max} (neat)/cm^{-1}: 3391 s br, 3236, vs, 3034 w, 2982 w, 2942 w, 2886 w, 1494 m, 1454 s, 1388 m, 1313 m, 1262 w, 1215 m, 1150 m, 1128 s, 1108 s, 1061 s, 1031 m, 904 m, 799 w, 767 s, 706 vs, 608 w. ^{1}H NMR (500.13 MHz, CD_3OD): $\delta_H = 1.65$ [d, $J = 7.0$, 3H, (CH_3)CH], 3.67–3.74 (m, 1H, >NCH^AH$^B_{(ring)}$), 4.20 and 4.67 (AB, $J_{AB} = 13.3$, 2H, CH_2Ph), 4.41–4.47 [m, 1H, CH(OH)], 4.49–4.53 (m, 1H, >NCH$^A H^B_{(ring)}$), 4.61 and 4.80 (AB, $J_{AB} = 13.0$, 2H, CH_2Ph), 4.74 [q, $J = 7.4$, 1H, (CH$_3$)CH], 7.46–7.48, 7.53–7.85, 7.69–7.75 (3m, 10H, (C$H_{(aromatic)}$). ^{13}C NMR (125.76 MHz, CD_3OD): $\delta_C = 12.21$ 61.01 and 63.52 (CH_2Ph), 63.65 (>N$CH_{2(ring)}$), 78.78 [CH(OH)], 129.37, 129.40, 130.58, 130.73, 131.71 ($C_{(aromatic)}$, 134.022, 134.091 ($C_{(aromatic\ ipso)}$). MS (FAB): 268.2 $(M-Br)^+$ (100%).

(2*S*,3*S*)-1,1-Dibenzyl-3-hydroxy-2-methylazetidinium bromide 2 was obtained as a crude product of de >70%; it was purified by column chromatography (silica gel 60) and the fraction of de >98% was used for further reactions. Yield: 35%, pale yellow solid. $[\alpha]_D^{20} = +21.3$ (*c* 1.1, MeOH). ^{1}H NMR (500.13 MHz, CD_3OD): $\delta_H = 1.52$ [d, $J = 7.0$, 3H, (CH_3)CH], 4.19–4.27 [m, 1H+2H,(CH$_3$)CH, >N$CH_{2(ring)}$], 4.26 and 4.58 (AB, $J_{AB} = 13.3$, 2H, CH_2Ph), 4.60 and 5.04 (AB, $J_{AB} = 13.0$, 2H, CH_2Ph), 5.02–5.08 [m, 1H, CH(OH)], 7.51–7.59 (m, 10H, (C$H_{(aromatic)}$). ^{13}C NMR (50.33 MHz, CD_3OD): $\delta_C = 8.62$ (CH_3), 61.43 and 63.43 [N(C_2Ph)$_2$], 64.39 (>N$CH_{2(ring)}$), 65.80 [CH(CH$_3$)], 76.60 [CH(OH)], 129.43, 129.62, 130.58, 130.63, 131.52, 131.79, 133.76, 134.00 ($C_{(aromatic)}$. MS (FAB): 268.0 $(M-Br)^+$ (100%). HRMS(FAB) [$(M-Br)^+$]: $C_{18}H_{22}NO$: Calcd: 268.1701. Found: 268.1701.

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14. *General remark*: The quoted yields are for homogenous (>98%, according to ^{31}P, ^{1}H, ^{13}C NMR) materials, isolated by column chromatography (silica gel 60) or recrystallization. **(2*R*,3*S*)-*O*,*O*-Diethyl-*S*-(3-*N*,*N*-dibenzylamino)-2-hydroxybutyl dithiophosphate 6**. 3-Hydroxyazetidinium salt **1** and sodium dithiophosphate **5a** were dissolved in DMF and left standing at room temperature for 48 h. The solvent was evaporated under high vacuo. Into the residue was added water and the reaction product extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$, concentrated and purified by column chromatography (eluent $CHCl_3$). Yield: 64%, (colourless oil). $[\alpha]_D^{20} = -8.2$ (*c* 0.2, MeOH). R_f 0.17 (CH_2Cl_2–MeOH, 40:1). IR (film): ν_{max} (neat)/cm^{-1}: 3480 w br, 3028 w, 2981 m, 2934 m, 2805 w, 1667 w, 1494 m, 1453 m, 1389 m, 1242 w, 1158 m, 1095 m, 1014 s, 958 s, 791 vs, 699 s, 660 s. ^{31}P NMR (80.96 MHz, $CDCl_3$): $\delta_P = 96.3$. ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta_H = 1.10$ [d, $J = 6.7$, 3H, (CH_3)CH], 1.25 [2 × t degradated into quin, $J = 7.1$, 6H, (CH_3CH$_2$O)$_2$], 2.59–2.68 [m, 1H+1H, CH^AH^{B}S–P, (CH$_3$)CH], 3.33 and 3.66 (AB, $J_{AB} = 13.6$, 4H, CH_2Ph), 3,44–3.51 [m, 1H, CH^{A}H^{B}S-P], 3.72–3.75 [m, 1H, CH(OH)], 4.01–4.11 [m, 4H, (CH$_3$CH_2O)$_2$], 7.14–7.27 (m, 10H, (C$H_{(aromatic)}$). ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta_C = 8.56$ [(CH_3)CH], 15.81 [d, $J_{C-P} = 8.80$, (CH_3CH$_2$O)$_2$], 39.44 (d, $J_{C-P} = 2.5$, CH_2S), 54.31 (CH_2Ph), 57.28 [(CH$_3$)CH], 63.13 [d, $J_{C-P} = 5.0$, (CH$_3$CH_2O)$_2$], 72.75 [CH(OH)], 126.99, 128.25, 129.07 (C$H_{(aromatic)}$), 139.50 (C-*ipso*). MS (FAB): 454.2 (M^++1). HMRS (FAB): $C_{24}H_{32}NO_4S_2P$+H: Calcd: 454.1639. Found: 454.1629.

(2*S*,3*S*)-*O*,*O*-Di-*n*-propyl-*S*-(3-*N*,*N*-dibenzylamino)-2-hydroxybutyl dithiophosphate 7 was prepared according to the procedure described above starting from (2*S*,3*S*)-*N*,*N*-dibenzyl-3-hydroxy-2-methylazetidinium bromide **2** and ammonium *O*,*O*-di-*n*-propyl phosphoroditioate. Yield: 65%, (colourless oil). $[\alpha]_D^{20} = +17.9$ (*c* 2.0, MeOH). R_f 0.18 (CH_2Cl_2–MeOH, 40:1). IR (film): ν_{max}(neat)/cm^{-1}: 3400 wbr, 3028 w, 2967 s, 2936 m, 2842 w, 1494 w, 1454 m, 1306 w, 1251 w, 1145 m, 1054 m, 985 vs, 910 w, 848 m, 750 s, 700 m, 664 s. ^{31}P NMR (80.96 MHz, $CDCl_3$): $\delta_P = 96.9$. ^{1}H NMR (200.13 MHz, $CDCl_3$): $\delta_H = 1.14$ and 1.15 [2 × t, $J = 7.3$, 6H, (CH_3CH$_2$CH$_2$O)$_2$], 1.11 [d, $J = 6.7$, 3H, (CH_3)CH], 1.59–1.78 [m, 4H, (CH$_3$CH_2CH$_2$O)$_2$], 2.61–2.85 [m, 1H+1H, CH^AH^{B}S, (CH$_3$)CH], 3.07–3.25 (m, 1H, CH^{A}H^{B}S), 3.34 and 3.87 (AB, $J_{AB} = 13.3$, 4H, CH_2Ph), 3.65–3.77 [m, 1H, CH(OH)], 3.90–4.13 [m, 4H, (CH$_3$CH$_2$CH_2O)$_2$], 7.20–7.40 (m, 10H, (C$H_{(aromatic)}$). ^{13}C NMR (75.43 MHz, $CDCl_3$): $\delta_C = 8.18$ [(CH_3)CH], 10.10 (CH_3CH$_2$CH$_2$O), 23.25 (d, $J_{C-P} = 22.6$, CH$_3$CH_2CH$_2$O), 37.91 (d, $J_{C-P} = 5.0$, CH_2S), 53.30 (CH_2Ph), 57.22 [(CH$_3$)CH], 69.32 (d, $J_{C-P} = 17.61$, CH$_3$CH$_2$C$_2$O), 70.38 and 70.49 [CH(OH)], 127.28, 128.18, 128.46, 128.91 (C$H_{(aromatic)}$), 138.41 (C-*ipso*). MS (FAB) $C_{24}H_{36}NO_3S_2P$+H: 482.3 (M^++1) (40%).

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19. **Sodium-(2*R*,3*S*)-3-*N*,*N*-dibenzyl-2-hydroxybutanethiosulfonate 11**. Yield: 50%, pale yellow solid. $[\alpha]_D^{20} = -5.5$ (*c* 0.7, MeOH). IR (KBr): ν_{max} (neat)/cm^{-1}: 3423 s br, 3027 w, 2931 w, 2839 w, 1637 w, 1495 w, 1139 s, 1074 w, 1028 s, 1004 s, 759 m, 698 m, 648 m, 534 w. ^{1}H NMR (500.13 MHz, CD_3OD): $\delta_H = 1.17$ [d, $J = 6.7$, 3H, (CH_3)CH], 2.74–2.80 [m, 1H, (CH$_3$)CH], 2.96 (dd, $J = 13.7$; 7.3, 1H, CH^AH^B–S), 3.31–3.34 (m, 1H, CH^{A}H^B–S), 3.43 and 3.87 (AB, $J_{AB} = 13.4$, 4H, CH_2Ph), 3.92 [td, $J = 5.2$, 7.8 [1H, CH(OH)], 7.22–7.39 (m, 10H, (C$H_{(aromatic)}$). ^{13}C NMR (125.76 MHz, CD_3OD):

δ_C = 8.905 [(*C*H$_3$)CH], 39.95 (*C*H$_2$–S), 54.66 (*C*H$_2$Ph), 58.40 [(CH$_3$)*C*H], 72.41 [*C*H(OH)], 128.29, 129.46, 130.17 (*C*H$_{(aromatic)}$), 140.17 (C-*ipso*). MS (FAB): 426.2 (M^++Na). HMRS (FAB): $C_{18}H_{22}NO_4S_2Na$+Na: Calcd: 426.0786. Found: 426.0778.

Sodium-(2*S*,3*S*)-(3-*N*,*N*-dibenzyl-2-hydroxybutanethiosulfonate 10. Yield: 63%, pale yellow solid. The specific rotation has not been measured because of the turbidness of the solution. IR (KBr): ν_{max} (neat)/cm^{-1}: 3422 s br, 2929 w, 1636 m, 1541 w, 1456 m, 1129 vs, 1004 s, 750 m, 698 m, 646 m, 538 w. ^{1}H NMR (500.13 MHz, CD_3OD): δ_H = 1.40 [d, *J* = 6.6, 3H, (C*H*$_3$)CH], 2.59–2.64 [m, 1H, (CH$_3$)C*H*], 2.80 (dd, *J* = 14.2; 9.0, 1H, C*H*^{A}H^B–S), 3.74 and 3.39 (AB, J_{AB} = 13.3, 4H, C*H*$_2$Ph), 3.81 (dd, *J* = 14.2; 3.0, 1H, CH^A H^B–S), 4.00 [td, *J* = 8.7; 2.90, 1H, C*H*(OH)], 7.18–7.23, 7.27–7.31, 7.34–7.38 (3 × m, 10H, (C*H*$_{(aromatic)}$). ^{13}C NMR (125.76 MHz, CD_3OD): δ_C = 8.85 [(*C*$_3$)CH], 41.79 (*C*H$_2$–S), 55.11 (*C*H$_2$Ph), 58.65 [(CH$_3$)*C*H], 73.83 [*C*H(OH)], 127.88, 129.22, 130.28 (*C*H$_{(aromatic)}$), 141.33 (C-*ipso*).