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Diastereoselective synthesis of β-aminocyclopentene sulfonic acid via hetero Diels–Alder reaction

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Abstract—A new cyclopentene GABA analogue was synthesized as a conformationally rigid analogue of the epilepsy drug vigabatrin. *N*-Sulfinyl dienophile Diels–Alder methodology, followed by alkaline hydrolysis of the corresponding dihydrothiazine oxide, oxidation and deprotection of the amino group gave *cis*-4-aminocyclopent-2-ene-1-sulfonic acid. The corresponding *N*,*N*-dimethylsulfinamide was also obtained.

1. Introduction

γ-Aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters in the mammalian central nervous system (CNS).[1] The enzyme that catalyzes the degradation of GABA, GABA aminotransferase (GABA-AT, EC 2.6.1.19), is a pyridoxal 5′-phosphate (PLP)-dependent enzyme.[2] Inhibition of this enzyme results in an increase in the availability of GABA, which can have a beneficial effect on neurological disorders including epilepsy,[3] Parkinson's disease,[4] Huntington's chorea[4b,5] and Alzheimer's disease.[6]

Some years ago several cyclopentene GABA analogues were synthesized as conformationally rigid analogues of the epilepsy drug vigabatrin.[7] As part of an ongoing project aimed to design and to develop an inactivator of the GABA-AT,[8] we present a diastereoselective synthesis of a new sulfonic amino acid: *cis*-4-aminocyclopent-2-ene-1-sulfonic acid **1** (Fig. 1).

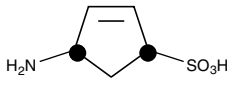

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Figure 1.

Keywords: GABA-AT; *N*-Sulfinyl dienophile Diels–Alder methodology; Aminocyclopentene sulfonic acid; Performic acid.
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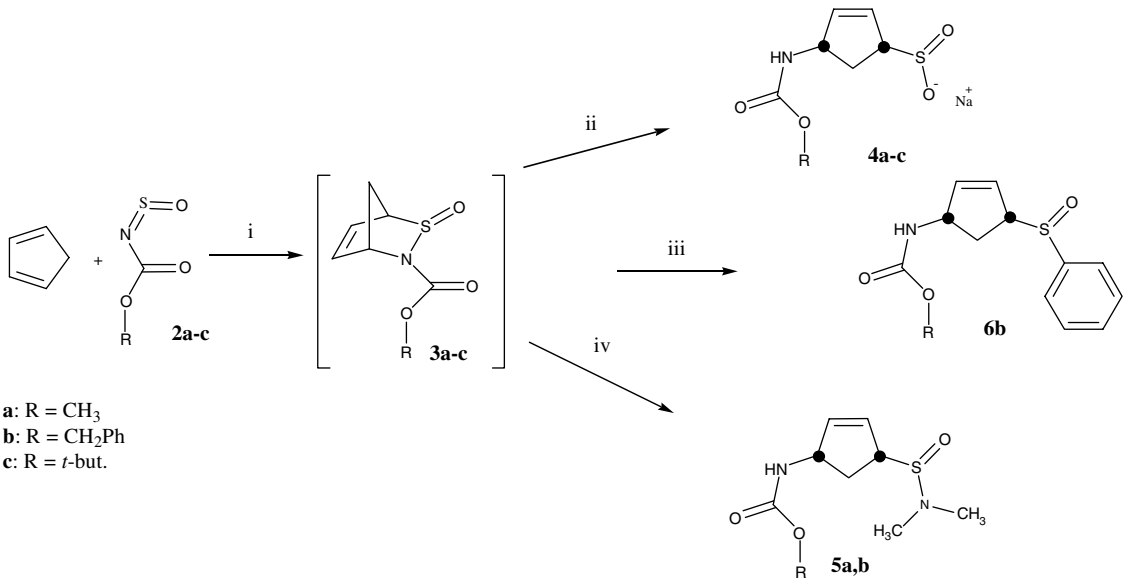
2. Results and discussion

The preparation of **1** was carried out by *N*-sulfinyl dienophile Diels–Alder methodology.[9] The first step is the cycloaddition of cyclopentadiene and *N*-sulfinyl carbamate **2a**–**c** (these compounds were obtained following a published procedure).[10] This reaction could be effected at 0 °C in toluene to afford cycloadducts **3a**–**c** in high yield. Since at room temperature and/or upon attempted chromatographic purification **3** was subject to retro Diels–Alder reaction, it was immediately treated with the nucleophilic agent.[11]

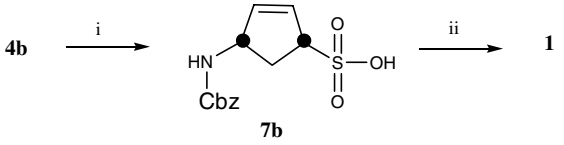
It is reported that the S–N bond in 3,6-dihydrothiazine oxide frame can be opened with several nucleophilic agents.[12,13] In fact, compounds **3a**–**c** smoothly reacted with Grignard reagents or sodium hydroxide to give compounds **6b**[10b] or **4a**–**c**, respectively, and, in addition, they were very susceptible to cleavage by nitrogen nucleophiles, affording sulfinamides **5a**,**b** (Scheme 1).[13]

In the first part of the project three different carbamates were used, and each of them is marked by a suitable characteristic: the most stable is the methylcarbamate, while the *tert*-butylcarbamate provides an easily cleavable protecting group for the amine. Finally, the benzylcarbamate shows intermediate reactivity with respect to methyl and *tert*-butylcarbamate, so from this point on, for the synthesis of **1**, we chose to use only the Cbz as a protecting group. Subsequently, the sulfinic function must be oxidized. Sulfinic acids are known to be readily oxidized, but the oxidation of our organic

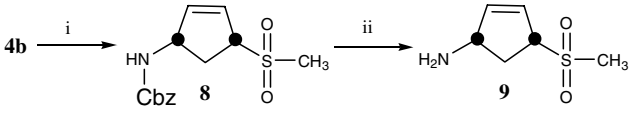


Scheme 1. Reagents and conditions: (i) PhMe, 0 °C, 20 h; (ii) NaOH, 1 equiv, THF, −60 °C, 15 min; (iii) PhMgBr 1 equiv, THF, −60 °C, 15 min; (iv) $NH(CH_3)_2$ 1 equiv, THF, −60 °C, 15 min.

substrate by molecular oxygen, even if very clean and devoid of by-products, required a long reaction time. The process was accelerated by the presence of Cu^{2+},[14] but in this case, in addition to oxidation, an undesired rearrangement to 3,3a,4,6a-tetrahydro-cyclopentaoxazol-2-one[10a] was observed. Therefore, we found out that the most convenient route was the procedure of Kresze et al.[15] Thus, upon treatment of **4b** with performic acid, allylic sulfonic acid **7** was easily obtained. Finally, the selective procedure for the cleavage of the carbamate moiety employed the use of dry hydrogen bromide in glacial acetic acid[16] (Scheme 2).[17] This reaction represents a nonhydrolytic cleavage and not a reduction process. Compound **1** (as a racemic mixture) was obtained in good yield after ion exchange chromatography. It is to be noted that, at least in strictly anhy-

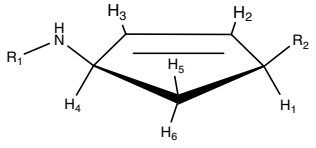


Scheme 2. Reagents and conditions: (i) HCO_3H, rt, 3 days; (ii) HBr/AcOH, rt, 1 h.



Scheme 3. Reagents and conditions: (i) CH_3I, rt, CH_3OH; (ii) HBr/AcOH, rt, 1 h.

Table 1. Selected ^1H NMR (200 MHz, CD_3OD, 28 °C) chemical shift (δ) and spin–spin coupling constants (J) values of amino cyclopentene derivatives



No.	R_1	R_2	Chemical shift (ppm)				Spin–spin coupling constants (Hz)		
			H_6	H_5	H_1	H_4	J_{gem}	J_{trans}	J_{cis}
1	H	$SO_3^-Na^+$	2.28	2.58	4.06	4.30	16.1	8.0	0.9
4b	Cbz	$SO_2^-Na^+$	1.56	2.28	3.12	4.45	14.6	8.7	2.8
4c	*t*-Boc	$SO_2^-Na^+$	1.71	2.64	3.94	4.74	14.0	8.4	4.3
5a	MeOCO	$SONMe_2$	2.18	1.63	3.81	4.78	14.9	3.9	2.5
5b	Cbz	$SONMe_2$	2.05	1.61	4.00	4.70	16.0	5.2	4.4
7b	Cbz	$SO_3^-Na^+$	1.71	2.64	3.90	4.74	14.0	8.4	4.3
10	H	CO_2H	2.08	2.63	3.72	4.38	15.1	8.7	4.3

Other signals δ: (**1**) 6.13 (m, 1H, H_3), 6.32 (m, 1H, H_2); (**4b**) 5.08 (s, 2H, OCH_2Ph), 5.82 (br s, 2H, H_2–H_3), 7.28 (s, 5H, C_6H_5); (**4c**) 1.53 (s, 9H, $(CH_3)C$), 5.91 (m, 1H, H_3), 6.14 (m, 1H, H_2); (**5a**) 2.70 (s, 6H, $N(CH_3)_2$), 3.65 (s, 3H, OCH_3), 5.91 (m, 2H, H_2–H_3); (**5b**) 2.75 (s, 6H, $N(CH_3)_2$), 5.21 (s, 2H, $PhCH_2O$), 5.92 (m, 2H, H_2–H_3), 7.3 (m, 5H, C_6H_5); (**7b**) 5.0 (s, 2H, $PhCH_2O$), 5.8 (br s, 2H, H_2–H_3), 7.3 (br s, 5H, C_6H_5).

drous conditions, addition reaction on the double bond was not observed.

Following this synthetic protocol a variety of N- and S-substituted derivatives can be obtained. As an example, the methyl sulfone **9**[18] was obtained upon treatment of **4b** with iodomethane to afford **8**, followed by the usual carbamate cleavage by dry hydrogen bromide in glacial acetic acid[16] (Scheme 3). It is noteworthy that further molecular diversity could be obtained on the basis of the 2,3-double bond reactivity.

The stereochemistry of Diels–Alder products is largely predictable on the basis of the cycloaddition mechanism. Furthermore, the structures of all new compounds were unequivocally confirmed by mono- and two-dimensional ^{1}H and ^{13}C NMR spectra.[19] In particular, the cis-stereochemistry of 1- and 4-hydrogens in compound **1** was confirmed by NOESY experiment. In addition, the coupling constants of compounds **1**, **4b**,**c**, **5a**,**b**, **7b** are in agreement with the corresponding data for *cis*-4-amino-2-cyclopentene-1-carboxylic acid **10**, prepared according to Allan and Fong.[20] The small differences found can be attributed to steric effects of the substituents on the nitrogen and sulfur atoms affecting the cyclopentene conformation (Table 1).

3. Conclusion

In summary, to our knowledge, this work describes the first example of synthesis of sulfonic amino acid using hetero Diels–Alder reaction followed by nucleophilic cleavage as the key step. This strategy is suitable for synthesizing polyfunctionalized systems. We are currently extending this approach to other cyclic systems. Investigation on biological activity is also in progress.

Acknowledgements

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13. *Typical procedure for the synthesis of compounds* **4**, **5** *and* **6**. A solution of *N*-sulfinylcarbamate (28.4 mmol) in anhydrous toluene (5 mL) at 0 °C was added to freshly cracked cyclopentadiene (1.92 mL, 28.4 mmol), and the mixture was stirred at 0 °C for 20 h. THF (40 mL) was added, the crude product was divided into three parts and each was cooled to −60 °C. In the first one, phenyl magnesium bromide (9.4 mL, 9.4 mmol, 1.0 M in THF) was added and the mixture was stirred for 15 min. The reaction mixture was diluted with saturated aqueous NH_4Cl (15 mL) and extracted with ether (3 × 10 mL). The organic layer was washed with brine and dried ($MgSO_4$). Concentration of the organic phase in vacuo yielded cis-allylic sulfoxide **6** (8 mmol, 85% yield) as a yellow oil. In the second, sodium hydroxide (0.376 g, 9.4 mmol), solubilized in the minimal water amount, was added dropwise and the mixture was stirred for 15 min. The solution was evaporated in vacuo, solubilized in 10 mL of water and submitted to an easy workup by extraction with ether (2 × 10 mL). Concentration of the aqueous phase in vacuo yielded **4** as a yellow solid (8.46 mmol, 90% yield). In the last part Me_2NH (2.5 mL, 9.4 mmol, 3.7 M in benzene) was slowly added and the mixture was stirred for 15 min. Then the solution was concentrated under reduced pressure, the crude product was purified by flash chromatography eluting first with AcOEt and then with MeOH to give **5** as a brown solid (8.65 mmol, 92% yield).
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17. *Synthesis of compound* **1**. A solution was prepared from 30 mL of 98% formic acid and 10 mL of acetic anhydride. In 8 mL of this solution were dissolved 1.15 g (3.8 mmol) of **4b** and 1.15 g (10.2 mmol) of 30% hydrogen peroxide. The reaction mixture was allowed to stand at room temperature for 3 days. The solution was evaporated under vacuo to give 0.971 g (3.27 mmol, 86% yield) of allylic sulfonic acid **7**. A solution (15 mL) of dry hydrogen bromide (33% min) in glacial acetic acid was added to **7** (0.971 g, 3.27 mmol as dry powder) in a reaction flask protected from moisture. Immediately after the addition of the reagent, carbon dioxide began to develop and the mixture was stirred at room temperature for 1 h. The solution was carefully evaporated under nitrogen flow, the

residue was purified with an ion-exchange column (Dowex AG 50w-8x, H^+ form), eluting with MeOH and then with water. Evaporation of solvents afforded **1** as a yellow solid (0.469 g, 2.88 mmol, 88%).

18. *Synthesis of compound* **9**. To a solution of **4** (1.82 g, 6 mmol) in 10 mL of MeOH was added 0.37 mL (6 mmol) of iodomethane and the mixture was stirred at room temperature for 3 h. The crude product was purified by flash chromatography eluting with AcOEt to give **8** as a yellow oil (1.28 g, 4.35 mmol, 72.5% yield). **9** was obtained by similar deprotection procedure used for **1**.[16]
19. All new compounds gave satisfactory (within 0.3%) analytical data. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 200 spectrometer at 200 and 50 MHz, respectively. ^{13}C assignment were established based on ^1H–^{13}C 2D heterocorrelation experiments. NOESY experiment was carried out on a Bruker AVANCE 400 NMR instrument. ESI MS spectra were obtained with a LCQ-DECA Thermo Finnigan instrument. IR spectra were obtained with a Perkin Elmer Spectrometer BX FT-IR. Spectral data are given as follows:
(Z) 4-Methoxycarbonylamino-cyclopent-2-ene sodium sulfinate **4a**: mp over 300 °C; ^1H NMR (CD_3OD) δ: 1.82 (m, 1H, cis H_5), 2.33 (m, 1H, trans H_5), 3.25 (br s, 1H, H_1), 3.61 (br s, 3H, OCH_3), 4.61 (m, 1H, H_4), 5.91 (m, 2H, H_2–H_3); MS (ESI), *m*/*z*: 204 (M^-).
(Z) 4-Benzyloxy-carbonylamino-cyclopent-2-ene sodium sulfinate **4b**: mp over 300 °C; ^{13}C NMR (CD_3OD) δ: 30.6 (C_5), 56.9 (C_4), 67.3 (C_1), 74.8 ($PhCH_2O$), 127.4 (C_2), 127.9 (C_3), 129.0 (Ph), 131.0 (Ph), 136.0 (Ph), 138.2 (Ph), 157.7 (NCOO); MS (ESI), *m*/*z*: 280 (M^-).
(Z) 4-tert-Butoxy-carbonylamino-cyclopent-2-ene sodium sulfinate **4c**: decomp. before melting; ^{13}C NMR (CD_3OD) δ: 28.4 (CH_3), 30.9 (C_5), 56.6 (C_4), 72.5 (C_1), 80.5 ($(Me)_3CO$), 129.6 (C_3), 139.1 (C_2), 156.0 (NCOO); MS (ESI), *m*/*z*: 246 (M^-).
(Z) Dimethylsulfinamoyl-cyclopent-2-enyl-4-carbamic acid methyl ester **5a**: ^{13}C NMR (CD_3OD) δ: 30.5 (C_5), 37.5 (Me_2N), 51.8 (C_4), 57.7 (C_1), 66.5 (CH_3O), 128.0 (C_3), 136.8 (C_2), 155.7 (NCOO); MS (ESI), *m*/*z*: 255 $(M+Na)^+$.
(Z) Dimethylsulfinamoyl-cyclopent-2-enyl-4-carbamic acid benzyl ester **5b**: ^{13}C NMR (CD_3OD) δ: 32.8 (C_5), 37.7 (Me_2N), 50.2 (C_4), 57.5 (C_1), 68.0 (CH_2O), 128.5 (C_3), 129.1 (Ph), 130.3 (Ph), 136.0 (C_2), 137.3 (Ph), 138.2 (Ph), 157.0 (NCOO); MS (ESI), *m*/*z*: 332 $(M+Na)^+$.
(Z) Sodium 4-phenoxycarbonylamino-cyclopent-2-enesulfonate **7b**; mp over 300 °C; ^{13}C NMR (D_2O) δ: 34.5 (C_5), 57.1 (C_4), 67.3 (C_1), 75.6 (CH_2O), 129.0 (Ph), 131.0 (Ph),131.7 (C_3), 136.3 (C_2), 138.0 (Ph), 138.2 (Ph), 157.6 (NCOO); MS (ESI), *m*/*z*: 296 (M^-).
(Z) Sodium 4-amino-cyclopent-2-enesulfonate **1**; decomp. before melting; ^{13}C NMR (D_2O) δ: 32.3 (C_5), 56.7 (C_4), 66.7 (C_1), 132.8 (C_3), 136.9 (C_2); MS (ESI), *m*/*z*: 162 (M^-). IR (KBr) ν_{max} 3435.88, 1616.56, 1457.98, 1166.13, 1042.63, 707.70, 617.14.
(Z) (Methanesulfonyl-cyclopent-2-enyl)-4-carbamic acid phenyl ester **8**: yellow oil, ^1H NMR (CD_3OD) δ: 2.02 (dt, 1H, $J = 14.9$, 3.4 Hz, cis H_5), 2.73 (dt, 1H, $J = 14.9$, 9.1 Hz, trans H_5), 3.01 (s, 3H, CH_3SO_2), 4.33 (m, 1H, H_1), 4.71 (m, 1H, H_4), 5.12 (s, 2H, $PhCH_2O$), 6.01 (m, 2H, H_2–H_3), 7.32 (s, 5H, C_6H_5); ^{13}C NMR (CD_3OD) δ: 32.3 (C_5), 39.4 (CH_3SO_2), 56.8 (C_4), 67.4 (C_1), 129.0 (Ph), 129.8 (C_3), 131.1 (Ph), 137.5 (C_2), 138.1 (Ph), 138.2 (Ph), 157.5 (NCOO); MS (ESI), *m*/*z*: 318 $(M+Na)^+$.
(Z) Methanesulfonyl-cyclopent-2-enyl-4-amine **9**: oil, ^1H NMR (CD_3OD) δ: 2.31 (dt, 1H, $J = 15.2$, 2.5 Hz, cis H_5), 2.75 (dt, 1H, $J = 15.2$, 8.5 Hz, trans H_5), 3.12 (s, 3H, CH_3SO_2), 4.43 (m, 1H, H_1), 4.51 (m, 1H, H_4), 6.34 (br s, 2H, H_2–H_3); ^{13}C NMR (CD_3OD) δ: 30.3 (C_5), 39.3 (CH_3SO_2), 56.6 (C_4), 59.8 (C_1), 132.6 (C_3), 136.2 (C_2); MS (ESI), *m*/*z*: 162 $(M)^+$.
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