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STUDIES ON STRUCTURALLY SIMPLE α,β-BUTENOLIDES. VII. AN EASY ENTRY TO γ-THIOMETHYL- AND γ-AMINOMETHYL-α,β-BUTENOLIDES

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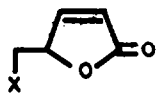
Abstract.- The reaction of the dilithium salt of phenylselenoacetic acid with a variety of glycidyl substrates yields 5-heteromethyl-3-phenylseleno-tetrahydrofuran-2-ones. Selective oxidation of the selenium atom allows the preparation of 5-thiomethyl- and 5-aminomethyl-2-(5H)-furanones.

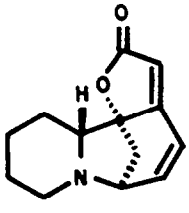
INTRODUCTION

Our interest in the synthesis of γ-heteromethyl substituted α,β-butenolides, 1, as potential antiviral and bacteriostatic molecules, and as synthons for the construction of more complex structures, has led us to the design of several synthetic pathways for this kind of compound.[1,2,3] While γ-alkoxymethyl-α,β-butenolides can be easily prepared from D-ribonolactone[2] or L-glutamic acid,[4] there are no general procedures to obtain compounds of type 1, X=SR or NRR'.



X=OR
SR
NRR'

1



2

We have already shown that substitution reactions on easily available γ-hydroxymethyl- or γ-bromomethyl-α,β-butenolides compete strongly with an elimination reaction that yields protoanemonin (γ-methylene-α,β-butenolide).[3] On the other hand, although this last substance gives in some cases 1,6-addition reactions, e.g. with phenylthiol, the procedure is not general since very complicated mixture crudes are obtained, especially in the case of nitrogen nucleophiles.[5]

However, another approach could be envisaged where the butenolide is formed through two moieties, one of them already carrying the heteroatom portion X and the other being an acetic acid synthon. We have used this approach by condensation of glycidyl ethers with diethyl malonate, and

after a long sequence the double bond of the butenolide was created.[1] Unfortunately this method could not be used for sulfur or nitrogen derivatives.

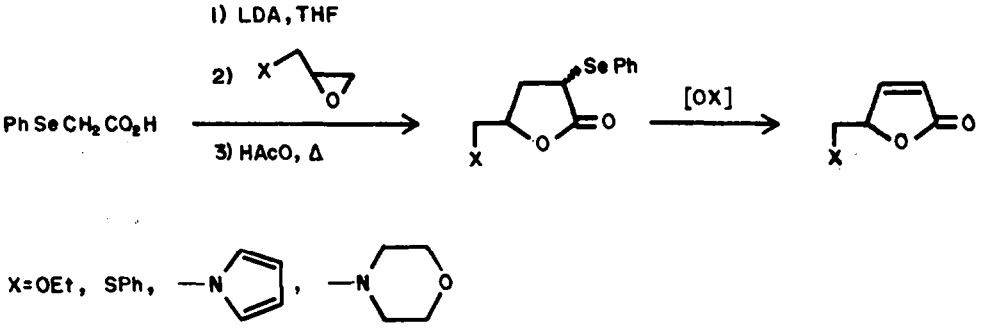
Nitrogen substituted butenolides of type 1 were then very reluctant to be synthesized. A bibliographic revision showed us that only three references exist on compounds of this type with a hydrogen atom in the γ position, although the butenolide ring is additionally substituted in α and/or β positions with electronegative atoms (halogen, OH or OMe).[6,7,8] All other δ-nitrogen substituted butenolides found have the γ position difunctionalized with alkyl chains, as for example in the alkaloids of the securinega type, e.g. securinine 2.[9]

From our studies[1] it seemed clear that the presence of a γ-hydrogen and a basic δ-nitrogen in a same α,β-butenolide would make very unstable these substances. However, it is important to show if this kind of compounds can exist and if they are the first intermediates in the reaction of protoanemonin with amines since the pharmacological activity of this γ-methylene-α,β-butenolide has been atributed to its reaction with the amine residues of the cell proteines. Therefore an easy, rapid and mild method for the synthesis of butenolides of type 1 was necessary.

We thought that the epoxide methodology could be further explored, especially having in mind that the reaction of the dilithium salt of phenylthioacetic acid with oxiranes has already been used in the synthesis of butenolides.[10] We show herein that the dilithium salt of phenylselenoacetic acid also reacts with glycidyl ethers, thioethers or amines in good yields affording the corresponding α-phenylselenobutanolides. The selective oxidation, in very mild conditions,[11] of the selenium atom has allowed us the preparation of 1, X=SR or NRR'. While this work was completed, Hanessian et al. published a note[12] in the same sense although no δ-sulfur nor δ-nitrogen substituted α,β-butenolides were described using this methodology.

RESULTS AND DISCUSSION

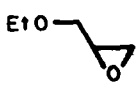
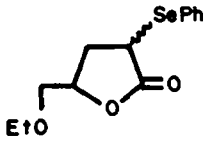
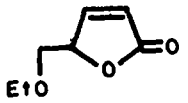
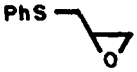
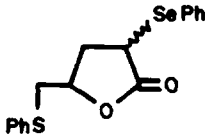
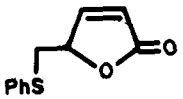
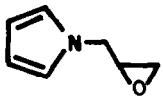
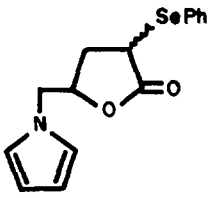
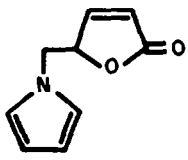
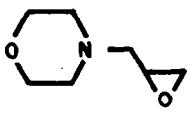
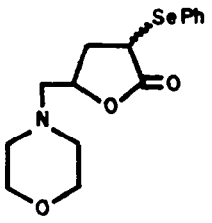
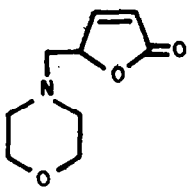
Scheme 1 shows the steps utilised in our synthetic approach to γ-heteromethyl-α,β-butenolides containing oxigen, sulfur or nitrogen in the δ-position.



Scheme 1

Reaction of the dianion of phenylselenoacetic acid (prepared with lithium diisopropylamide, LDA) with the appropriate epoxide (3-6) in tetrahydrofuran, followed by acidification and heating at the reflux temperature, afforded diastereoisomeric mixtures of lactones 7-10 in good yields (Table 1).[13] Since after oxidation both the trans and cis isomers will lead to the same butenolide, nó special efforts were made to separate each isomer.

Table 1

EPOXIDE	BUTANOLIDE	(% YIELD)	BUTENOLIDE	(% YIELD)
		(56)		(100)
3	7		11	
		(73)		(57)
4	8		12	
		(87)		(100)
5	9		13	
		(71)		(61)
6	10		14	

However, in the process of purification of the reaction crudes, pure samples of each diastereoisomer could be isolated for compounds 7, 9 and 10. Assuming that in this kind of molecules the unit C_5-O_1-C_2(O)-C_3 is nearly planar[14] (Figure 1) and considering the coupling constant values J_{34} and $J_{34'}$ experimentally obtained in each case, the less polar component of the mixture was

tentatively assigned to the trans isomer, and the more polar to the cis. In the cis isomer the clearly preferred conformation would be the one with the two bulky groups in equatorial positions (A). Considering the dihedral angles H_3-C_3-C_4-H_4 and H_3-C_3-C_4-$H_{4'}$, similar values of the coupling constants J_{34} and $J_{34'}$ should be expected, as it is the case in the PMR spectra of the more polar isomers. The different values of J_{34} and $J_{34'}$ observed in the PMR spectra of the less polar isomers can be explained assuming a similar contribution of both forms (C and D) in their conformational equilibrium. See experimental part for the respective J values.

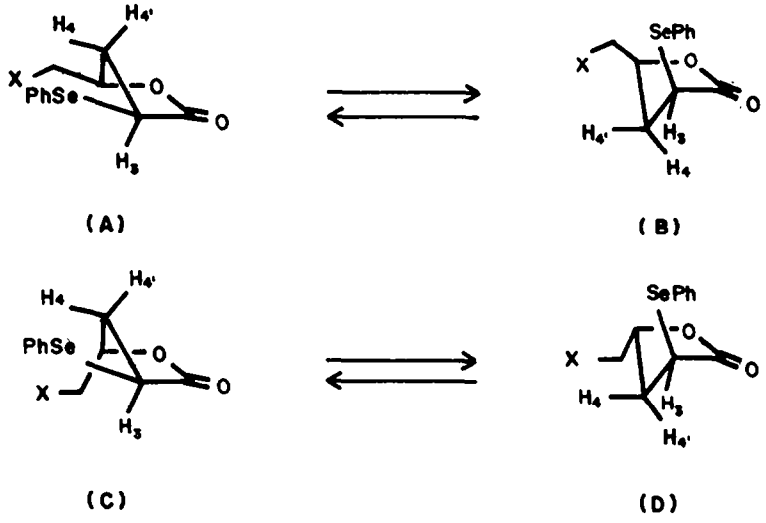


Figure 1

Oxidation of lactones 7 and 9 was performed with excess H_2O_2 following the standard described procedure[15] and since elimination of benzeneselenenic acid occurs simultaneously the corresponding new α,β-butenolides 11 and 13 were obtained. In spite of having a nitrogen atom in the δ position, 5-pyrrolidylmethyl-2(5H)furanone 13 proved to be a stable compound and no special precaution had to be taken to prepare or manipulate it.

When the selenium atom was not the only easily oxidable group present in the molecule (as it is the case in butanolides 8 and 10), the oxidation-elimination step had to be performed in different conditions. 5-Phenylthiomethyl-2(5H)furanone 12 and the new 5-(4-morpholinyl)methyl-2(5H)-furanone 14 were prepared by oxidation of the corresponding phenylselenobutanolides 8 and 10 respectively in a two phase system solvent.[16] Oxidation of 8 was effected with a slight excess of H_2O_2 in neutral medium, while a large excess of H_2O_2 in acidic medium was used to oxidize lactone 10. Butenolide 14 can be handled in acidic solutions or as its hydrochloride and was identified as a base by its spectroscopical data. However, in this state it decomposes rapidly to give protoanemonin.

Thus, we show in this paper that using the procedure recently reported by Hanessian[12] α,β-butenolides 1 (X=NRR') have been obtained for the first time. These compounds are stable if the nitrogen atom is weakly basic as in 13, but when it has an aminic character, and can be easily eliminated as amine, the compound decomposes. This behaviour explains the lack of stability found for δ-aminotetronic lactones[7] and the stability observed for a more complex γ-aminomethyl-α,β-butenolide[8], where the elimination reaction can not give a γ-methylene-α,β-butenolide. Moreover our work presents, to the best of our knowledge, the first example of a carbon-carbon double bond creation by an oxidation-elimination procedure from a phenylselenium unit in the presence of a phenylsulfur moiety. We are extending this method to the synthesis of other γ-aminomethyl-α,β-butenolides, particularly to structures found in natural products.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer mod. 720 spectrophotometer, PMR and ^{13}C NMR spectra at 80 MHz and 20 MHz respectively on a Bruker WP-80 spectrometer, and mass spectra were performed under electron impact at 70 eV or chemical ionization (NH_3) on a Hewlett-Packard 5930 A spectrometer. Distillations were effected on a rotational distillator Büchi, mod. KRV 65/30 (only oven temperature given). Microanalyses were performed at Consejo Superior de Investigaciones Cientificas.

General procedure for the synthesis of 5-heteromethyl-3-phenylselenotetrahydrofuran-2-ones. A solution of phenylselenoacetic acid (432 mg, 2.0 mmole) in THF (2 ml) was added to a stirred solution of LDA (4.4 mmole) in THF (8 ml) at 0°C under argon and the mixture stirred for 1 h. Then a solution of epoxide (2.0 mmole) in THF (4 ml) was added, the reaction mixture let to warm to room temperature and stirred for 3 h. The cool slurry was acidified with glacial acetic acid, and heated at the reflux temperature for 6 h, then neutralized ($NaHCO_3$ saturated solution) and extracted with ether. The organic extracts were washed with water, dried (anh. Na_2SO_4) and the solvent removed yielding a crude material, wich was purified by flash column chromatography. All phenylselenobutanolides 7, 8, 9, and 10 were fully characterized by their spectroscopical data (see below). They are oil compounds very difficult to purify and, since we considered them as intermediates for the preparation of the corresponding α,β-butenolides, no effort was always made for purifying them enough to perform microanalysis.

5-Ethoxymethyl-3-phenylselenotetrahydrofuran-2-one **7**. Following the general procedure, from ethoxymethyloxirane **3** (204 mg, 2.0 mmole), after purification by flash column chromatography (CH_2Cl_2), 334 mg (1.12 mmole, 56% yield) of **7** were obtained. IR (film): $\bar{\nu}$ 3060 (w), 2980 (m), 2930(m), 2870 (m), 1760 (s), 1580 (w), 1470 (m), 1440 (m), 1380 (m), 1275 (m), 1170 (s), 1120 (s), 1060 (m), 1025 (m), 935 (m), 740 (s), and 690 (s) cm^{-1}. MS: *m/e* (%) 300 (M, 75.1), 272 (12.4), 213 (12.3), 185 (60.0), 157 (100.0), 87 (25.5), 77 (37.8), and 29 (40.9). Found: C, 51.91; H, 5.51. $C_{13}H_{16}O_3Se$ requires: C, 52.18; H, 5.39. Analytical samples of the *trans* (**7a**) and *cis* (**7b**) isomers could be separated. **7a**: PMR ($CDCl_3$): δ 7.78-7.59 (2H, m), 7.45-7.24 (3H, m), 4.44 (1H, m), 4.04 (1H, dd, J=8.2, J'=4.9), 3.52 (2H, q, J=6.7), 3.73-3.34 (2H, m), 2.44 (2H, m), and 1.15 (3H, t, J=6.8); ^{13}C NMR ($CDCl_3$): δ 175.4, 135.3, 129.1, 128.7, 126.8, 77.5, 71.2, 66.9, 36.6, 32.4, and 14.8. **7b**: PMR ($CDCl_3$): δ 7.78-7.57 (2H, m), 7.42-7.24 (3H, m), 4.56 (1H, m), 3.99 (1H, dd, J=9.8, J'=8.6), 3.49 (2H, q, J=7.0), 3.45 (2H, m), 2.45 (2H, m), and 1.17 (3H, t, J=6.9); ^{13}C NMR ($CDCl_3$): δ 175.6, 135.2, 129.2, 128.6, 127.8, 77.5, 71.3, 67.1, 36.8, 32.2, and 14.9. Acidification of the aqueous phase, followed by extraction with CH_2Cl_2 allowed us to recover 146 mg (0.46 mmole, 32%) of starting phenylselenoacetic acid.

5-Phenylthiomethyl-3-phenylselenotetrahydrofuran-2-one **8**. In the usual manner, from phenylthiomethyloxirane **4** (332 mg, 2.0 mmole), after purification by flash column chromatography (CH_2Cl_2) 529 mg (1.46 mmole, 73% yield) of **8** were obtained, as a mixture of the *trans* and *cis* isomers. PMR ($CDCl_3$): δ 7.74-7.16 (10H, m), 4.66-4.17 (1H, m), 4.10-3.84 (1H, m), 3.42-1.86 (4H, m). IR (film): $\bar{\nu}$ 3040 (m), 3000 (w), 2910 (m), 1750 (s), 1570 (m), 1470 (s), 1430 (s), 1330 (m), 1290 (m), 1170 (s), 1085 (m), 1065 (m), 1020 (s), 910 (m), 735 (s), and 685 (s) cm^{-1}. MS: *m/e* (%) 366 (2.1), 365 (2.1), 364 (M, 9.3), 362 (3.3), 207 (72.6), 157 (31.9), 155 (18.8), 123 (69.7), 109 (27.7), 77 (71.1), 65 (32.1), 55 (59.1), 51 (47.2), and 45 (100.0).

5-Pyrrolidylmethyl-3-phenylselenotetrahydrofuran-2-one **9**. In the above conditions, from pyrrolidylmethyloxirane **5** (246 mg, 2.0 mmole), after purification by flash column chromatography (EtAcO), 554 mg (1.73 mmole, 87% yield) of **9** were obtained. IR (film): $\bar{\nu}$ 3050 (w), 3000 (m), 2920 (m), 2880 (m), 1760 (s), 1500 (m), 1440 (m), 1360 (m), 1340 (m), 1300 (s), 1175 (s), 1100 (s), 1080 (m), 1040 (m), 940 (m), 840 (w), and 740 (s) cm^{-1}. MS *m/e* (%) 323 (4.5), 322 (5.3), 321 (M, 22.1), 320 (2.3), 319 (8.0), 318 (4.5), 317 (4.5), 213 (4.0), 212 (7.0), 164 (62.3), 157 (35.8), 118 (23.7), 80 (100.0), 77 (30.2), 53 (35.6), and 51 (25.8). Analytical samples of the *trans* (**9a**) and *cis* (**9b**) isomers could be isolated. **9a**: PMR ($CDCl_3$): δ 7.78-7.09 (5H, m), 6.61 (2H, t, J=2.4), 6.16 (2H, t, J=2.4), 4.56 (1H, m, J_1=9.1, J_2=5.3, J_3=4.0, J_4=3.6), 4.20 (1H, dd, J=-15.0, J'=3.6), 3.98 (1H, dd, J=-15.0, J'=4.0), 3.49 (1H, dd, J=4.8, J'=8.5), 2.28 (1H, ddd, J=4.8, J'=-16.9, J"=9.1), 2.27 (1H, ddd, J=8.6, J'=-16.9, J"=5.3) (This spectrum was partially simulated with a DANTE programm). ^{13}C NMR ($CDCl_3$): δ 174.7, 135.4, 129.3, 128.9, 126.6, 121.5, 109.2, 77.6, 52.0, 35.9, and 32.9. **9b**: PMR ($CDCl_3$): δ 7.76-7.12 (5H, m), 6.62 (2H, t, J=2.3), 6.15 (2H, t, J=2.3), 4.58 (1H, m), 4.03 (3H, m), and 2.33 (2H, m). ^{13}C NMR ($CDCl_3$): δ 174.7, 135.6, 129.3, 128.9, 126.7, 121.0, 109.0, 77.6, 52.4, 36.5, and 32.7.

5-(4-Morpholinyl)methyl-3-phenylselenotetrahydrofuran-2-one **10**. As in the preceeding runs, from 4-morpholinylmethyloxirane **6** (286 mg, 2.0 mmole), after purification by flash column chromatography (EtAcO), 508 mg (1.42 mmole, 71% yield) of **10** were obtained. IR (film): $\bar{\nu}$ 3050 (w), 2950 (m), 2920 (m), 2880 (m), 2850 (m), 2800 (m), 2680 (w), 1760 (s), 1570 (w), 1470 (m), 1445 (m), 1430 (m), 1350 (m), 1320 (w), 1280 (m), 1175 (s), 1140 (m), 1110 (s), 1065 (m), 1035 (m), 1020 (m), 1010 (m), 960 (w), 940 (m), 860 (s), 790 (w), 735 (s), and 690 (s) cm^{-1}. MS *m/e* (%) 341 (M, 3.8), 339 (1.2), 157 (8.9), 155 (4.5), 100 (100.0), 77 (8.0), and 42 (33.1). Analytical samples of the *trans* (**10a**) and *cis* (**10b**) isomers could be separated. **10a**: PMR ($CDCl_3$): δ 7.77-7.58 (2H, m), 7.46-7.22 (3H, m), 4.48 (1H, m), 3.99 (1H, dd, J=7.2, J'=4.0), 3.80-3.59 (4H, m), and 2.72-2.05 (8H, m). ^{13}C NMR ($CDCl_3$): δ 175.0, 135.1, 129.0, 128.6, 126.7, 77.1, 66.4, 61.6, 53.8, 36.2, and 34.2. **10b**: PMR ($CDCl_3$): δ 7.80-7.59 (2H, m), 7.46-7.23 (3H, m), 4.56 (1H, m), 3.99 (1H, dd, J=J'=9.3), 3.78-3.57 (4H, m), and 3.08-1.84 (8H, m). ^{13}C NMR ($CDCl_3$): δ 175.4, 135.4, 129.2, 128.7, 127.2, 77.2, 66.6, 62.2, 54.1, 36.7, and 34.0.

5-Ethoxymethyl-2(5H)-furanone **11**. A solution of 297 mg of **7** in THF (2 ml) at 0°C was treated with 3 drops of glacial acetic acid and 0.70 ml of 30% H_2O_2 and stirred at 0°C for 30 minutes. The reaction mixture was neutralized ($NaHCO_3$ saturated solution) and extracted with CH_2Cl_2. The organic extracts were washed with water, dried (anh. Na_2SO_4) and the solvents removed, yielding 145 mg of **11** (100% yield), bp 90°C/0.45 mm. PMR($CDCl_3$): δ 7.52 (1H, dd, J=5.8, J'=1.7), 6.17 (1H, dd, J=5.8, J'=2.0), 5.15 (1H, m), 3.66 (2H, m), 3.56 (2H, q, J=6.8), and 1.19 (3H, t, J=6.6). ^{13}C NMR ($CDCl_3$): δ 172.6, 154.0, 122.2, 82.2, 69.9, 67.2, and 14.7. IR (film): $\bar{\nu}$ 3090 (m), 2970 (m), 2870 (m), 1750 (s), 1600 (m), 1440 (m), 1380 (m), 1330 (m), 1270 (m), 1160 (s), 1100 (s), 950 (m), 925 (m), 885 (m), 860 (m), and 820 (s) cm^{-1}. MS: *m/e* (%) 112 (2.7), 98 (8.5), 97 (10.9), 96 (14.4), 84 (47.9), 83 (28.6), 68 (19.6), 59 (100), 55 (73.9), 54 (39.5), and 42 (49.5); *c.i.*: 177 (M+35) and 160 (M+18). Found: C, 58.99; H, 7.38. $C_7H_{10}O_3$ requires: C, 59.14; H, 7.09.

5-Phenylthiomethyl-2(5H)-furanone **12**. To a solution of 169 mg (0.46 mmole) of **8** in CH_2Cl_2 (1.5 ml), 30% H_2O_2 (0.87 mmole) was slowly added and the mixture stirred at room temperature for 15 minutes. Then water was added and the aqueous layer extracted with CH_2Cl_2. The organic extracts were washed with water, dried (anh. Na_2SO_4), and the solvent removed. Purification by flash column chromatography (CH_2Cl_2) afforded 54 mg (0.26 mmole, 57% yield) of **12**, identical to that described before.[1]

5-Pyrrolidylmethyl-2(5H)-furanone **13**. Oxidation of 479 mg (1.5 mmole) of **9** in the same conditions described for the synthesis of **11** afforded 247 mg (1.5 mmole, 100% yield) of **13**, bp 95°C/0.07 mm. PMR ($CDCl_3$): δ 7.34 (1H, dd, J=5.8, J'=1.6), 6.61 (2H, t, J=2.1), 6.14 (2H, t, J=2.2), 6.05 (1H, dd, J=5.8, J'=2.2), 5.22 (1H, m), and 4.22 (2H, d, J=5.0). ^{13}C NMR ($CDCl_3$): δ 171.9, 152.7, 122.9, 121.3, 109.1, 82.2, and 50.8. IR (film): $\bar{\nu}$ 3130 (w), 3000 (w), 2960 (w), 1765 (s), 1510 (w), 1300 (m), 1275 (m), 1170 (m), 1105 (m), 820 (m), and 740 (m) cm^{-1}. MS: *m/e* (%) 164 (M+1, 3.1), 163 (M, 36.2), 81 (5.8), and 80 (100). Found: C, 66.27; H, 5.59; N, 8.45. $C_9H_9NO_2$ requires: C, 66.25; H, 5.56; N, 8.58.

5-(4-Morpholinyl)methyl-2(5H)-furanone **14**. To a solution of 167 mg (0.49 mmole) of **10** in CH_2Cl_2 (3 ml) at 0°C, 15 drops CF_3CO_2H were added. The solution was carefully treated with 340 µl of 30% H_2O_2, keeping the temperature at 0°C. Then it was stirred at room temperature for 15 minutes. To eliminate the excess oxidant, 312 mg of $NaHSO_3$ were added to the cooled (ice bath) solution, this was basified ($NaHCO_3$ saturated solution) and extracted with CH_2Cl_2. The organic extracts were washed with water, dried (anh. Na_2SO_4) and the solvent removed, giving 55 mg (0.30 mmole, 61% yield) of **14**. This compound decomposes rapidly. PMR ($CDCl_3$): δ 7.49 (1H, dd, J=5.8, J'=1.3), 6.16 (1H, dd, J=5,8, J'=1.8), 5.15 (1H, m), 3.70 (4H, t, J=5.3), and 3.07-2.00 (6H, m). ^{13}C NMR ($CDCl_3$): δ 172.6, 154.9, 122.1, 81.8, 66.8, 60.6, and 54.1. IR (film): $\bar{\nu}$ 3000-2750 (m), 1740 (s), 1625 (w), 1440 (w), 1150 (m), 1110 (s), 1060 (w), 1005 (w), 860 (w), and 810 (w) cm^{-1}. MS: *m/e* (%) 101 (10.0). 100 (100), 70 (10.3), and 56 (15.8); *c.i.*: 184 (M+1), and 100. The chlorhydrate was prepared by bubbling HCl through a solution of freshly prepared **14** in CH_2Cl_2. In neither case an analytical sample for elemental analysis could be obtained.

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