*ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 11, pp. 1651–1654. © Pleiades Publishing, Ltd., 2007.*
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# New Captodative Polyheterofunctionalized Cyclopentenones from 2,3,5-Trichloro-4,4-dimethoxy-5-(2-methylfuran-3-yl)-cyclopent-2-en-1-one and Secondary Amines

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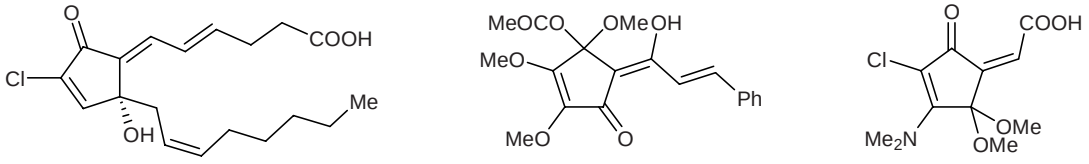
Received June 3, 2006; revised March 18, 2007

**Abstract**—2,3,5-Trichloro-4,4-dimethoxy-5-(2-methylfuran-3-yl)cyclopent-2-en-1-one reacted with secondary amines to give unusual $Ad_NE$-substitution–fragmentation products, 5-[(1*Z*,2*E*)-1-acetyl-3-dialkylaminoprop-2-en-1-ylidene]-3-dialkylamino-2-chloro-4,4-dimethoxycyclopent-2-en-1-ones.

**DOI:** 10.1134/S1070428007110115

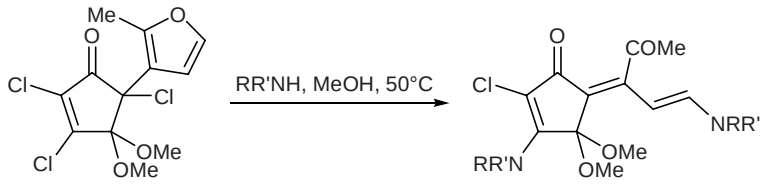
Compounds of the cyclopentenone series are widespread in nature, and they exhibit a broad spectrum of biological activity [1–3]. Among these, orthogonally functionalized cross-conjugated cyclopentenone derivatives attract specific interest, for combinations of even relatively simple structures (such as chlorovulones and prostaglandins [4], stigmahamones **II** and coruscanones [5], cryptosporiopsin [6] and compound **III** [7]) are quite promising from the viewpoint of pharmacology; in particular, compounds **I**–**III** are powerful anticarcinogenic, antibiotic, and antiviral agents. Previously described furyl-substituted trichlorocyclopentenone **IV** [8, 9] turned out to be a chemically rational starting compound in the design of such structures, especially taking into account the transformation **IV**→**V** which was demonstrated with a few examples [10] (Scheme 1). Structures **V** possess a cross-conjugated captodative trienedione system which is topologically related to the skeleton of compounds **I**–**III**, and they are exhaustively functionalized.

In the present work we examined the process shown in Scheme 1 in more detail with extension of the nucleophile series and variation of the conditions. Compound **IV** failed to react with sodium or potassium alkoxides and thiolates in tetrahydrofuran. Trichlorocyclopentenone **IV** was brought into reactions with other secondary amines under the conditions corresponding to the synthesis of **Va** and **Vb**. The struc-




**I** (Chlorovulone II) **II** (Stigmahamone I) **III**

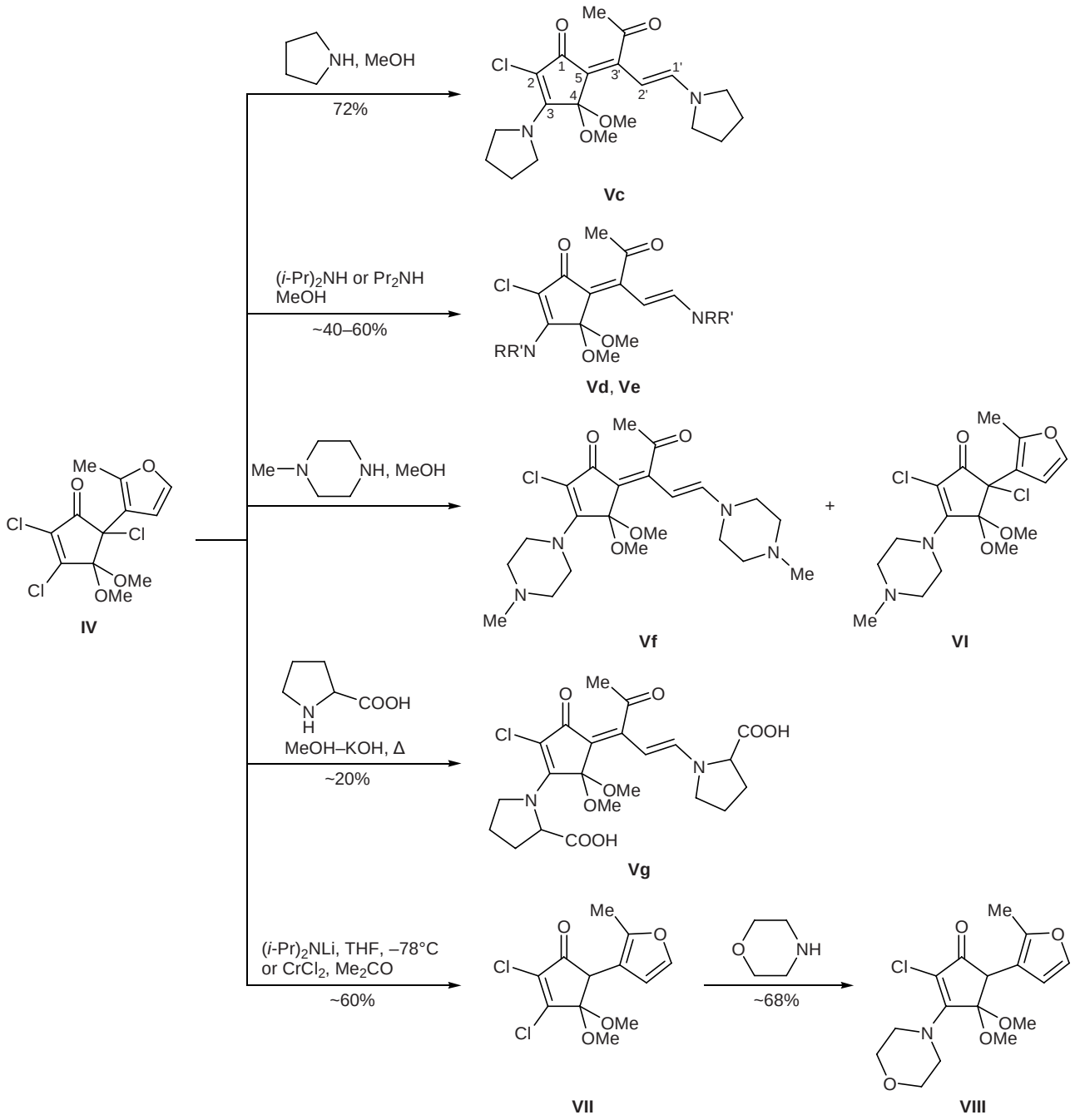
**Scheme 1.**




**IV** **Va**, **Vb**

R = R′ = Et (**a**), RR′N = morpholino (**b**).

**Scheme 2.**




**V**, R = R′ = *i*-Pr (**d**), Pr (**e**).

tures of new compounds **Vc**–**Vg** thus obtained are shown in Scheme 2.

Pyrrolidine turned out to be the most reactive nucleophile, and the corresponding product **Vc** was formed in a short time with a high yield. Likewise, compounds **Vd** and **Ve** were synthesized by reaction of **IV** with dipropylamine and diisopropylamine. Compounds **Vc**–**Vg** showed in the $^1$H NMR spectra signals from protons at the *trans*-configured double bond as doublets of doublets at δ 5.3–5.7 and 6.4–6.7 ppm ($J$ = 13–14 Hz), as well as a singlet at δ ~2.45 ppm from the methyl group. In the reaction with *N*-methylpiperazine, apart from the expected product **Vf**, we isolated its possible precursor, monoenamino derivative **VI**.

A probable mechanism of this transformation and stereochemistry of the double bonds in the products were discussed in [10]. We presumed that opening of the furan ring is favored by the presence of a chlorine atom on $C^5$. This assumption is confirmed by the fact that the furan ring in **VII** having no chlorine atom on $C^5$ remained intact in the reaction with morpholine, and the expected $Ad_NE$-substitution product **VIII** was obtained. Dichloro derivative **VII** was synthesized by treatment of ketone **IV** with $CrCl_2$ [11].

Reactions of compound **IV** with amino acids are difficult to occur. For example, L-proline derivative **Vg** was synthesized in a poor yield (~20%). Treatment of ketone **IV** with lithium diisopropylamide did not initiate its fragmentation, and only compound **VII** was formed as a result of reductive dechlorination at $C^5$.

Thus we have described a practical version of the design of a new series of pharmacologically interesting cross-conjugated cyclopentenones **V** containing oxygen, nitrogen, and chlorine atoms on the basis of compound **IV** and secondary amines.

## EXPERIMENTAL

The IR spectra were recorded on Specord M-80 and UR-20 spectrometers from samples prepared as thin films or dispersed in Nujol. The $^1H$ and $^{13}C$ NMR spectra were obtained on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively, from solutions in $CDCl_3$; the chemical shifts were measured relative to tetramethylsilane as internal reference. Thin-layer chromatography was performed on Silufol (Czech Republic) and Sorbfil plates (Russia); spots were visualized by treatment with iodine vapor or by spraying with a solution of *p*-methoxybenzaldehyde in ethanol containing sulfuric acid and subsequent heating to 120–150°C. The products were isolated by column chromatography on silica gel L (200–280 μm, Russia), sorbent-to-substrate ratio (30–60):1, freshly distilled solvents were used as eluents. Secondary amines were purified by drying over powdered potassium hydroxide, followed by distillation.

**5-[(*Z*,2*E*)-1-Acetyl-3-(pyrrolidin-1-yl)prop-2-en-1-ylidene]-2-chloro-4,4-dimethoxy-3-(pyrrolidin-1-yl)cyclopent-2-en-1-one (Vc).** A solution of 0.3 ml (3.4 mmol) of pyrrolidine in 5 ml of methanol was added dropwise under stirring to a solution of 0.30 g (0.92 mmol) of compound **IV** in 5 ml of methanol, and the mixture was stirred for 3 h at room temperature (until the initial compound disappeared according to the TLC data). The solvent was distilled off, 10 ml of cold water was added to the residue, and the mixture was extracted with chloroform (4×20 ml). The combined extracts were washed with a saturated aqueous solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:4) as eluent. Yield 0.26 g (72%), bright yellow crystals, mp 174–176°C. IR spectrum, ν, $cm^{-1}$: 956 (δCH=CH-*trans*); 1380 (δ$CH_3$); 1602 (C=C); 1660, 1703 (C=O). $^1H$ NMR spectrum, δ, ppm: 1.87 m (8H, $CH_2$), 2.46 s (3H, $CH_3$), 3.17 s (6H, $OCH_3$), 3.26 br.s (4H, $NCH_2$), 3.93 m (4H, $NCH_2$), 5.33 d (1H, 2′-H, *J* = 13.66 Hz), 6.69 d (1H, 1′-H, *J* = 13.69 Hz). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 25.0 ($CH_2$), 32.06 ($CH_3$), 45.21 ($NCH_2$), 51.41 ($OCH_3$), 90.82 ($C^{2'}$), 105.96 ($C^4$), 107.57 ($C^5$), 108.15 ($C^2$), 144.34 ($C^{1'}$), 147.66 ($C^{3'}$), 154.83 ($C^3$), 182.40 ($C^1$), 205.80 ($C^{4'}$). Found, %: C 60.32; H 6.73; Cl 9.50; N 6.79. $C_{20}H_{27}ClN_2O_4$. Calculated, %: C 60.83; H 6.89; Cl 8.98; N 7.09.

**5-[(*Z*,2*E*)-1-Acetyl-3-diisopropylaminoprop-2-en-1-ylidene]-2-chloro-3-diisopropylamino-4,4-dimethoxycyclopent-2-en-1-one (Vd)** was synthesized in a similar way from 0.26 g (0.80 mmol) of compound **IV** and 0.6 ml (3.5 mmol) of diisopropylamine. Yield 0.14 g (~40%), bright yellow needles, mp 118–120°C. IR spectrum, ν, $cm^{-1}$: 940 (δCH=CH-*trans*); 1370 (δ$CH_3$); 1600 (C=C); 1690, 1701 (C=O). $^1H$ NMR spectrum, δ, ppm: 1.25 d (24H, $CH_3$, *J* = 6.7 Hz), 2.47 s (3H, $CH_3$), 3.16 s (6H, $OCH_3$), 3.39 m (2H, NCH), 3.63 m (1H, NCH), 3.99 m (1H, NCH), 5.76 d (1H, 2′-H, *J* = 13.74 Hz), 6.79 d (1H, 1′-H, *J* = 13.10 Hz). Found, %: C 63.01; H 8.88; Cl 8.02; N 6.34. $C_{24}H_{39}ClN_2O_4$. Calculated, %: C 63.35; H 8.64; Cl 7.79; N 6.16.

**5-[(*Z*,2*E*)-1-Acetyl-3-dipropylaminoprop-2-en-1-ylidene]-2-chloro-3-dipropylamino-4,4-dimethoxycyclopent-2-en-1-one (Ve)** was synthesized in a similar way from 0.20 g (0.6 mmol) of compound **IV** and 0.6 g (5.9 mmol) of dipropylamine. Yield 0.16 g (~60%), dark yellow crystals, mp 93–94°C (from EtOAc–petroleum ether, 1:10). IR spectrum, ν, $cm^{-1}$: 950 (δCH=CH-*trans*); 1370 (δ$CH_3$); 1620 (C=C); 1665, 1701 (C=O). $^1H$ NMR spectrum, δ, ppm: 0.84 t (6H, $CH_3$, *J* = 7.3 Hz), 0.89 t (6H, $CH_3$, *J* = 7.6 Hz), 1.58 m (8H, $CH_2$, *J* = 7.3, 7.8 Hz), 2.44 s (3H, $CH_3$), 3.06 t (4H, $NCH_2$, *J* = 7.3 Hz), 3.14 s (6H, $OCH_3$), 3.65 t (4H, $NCH_2$, *J* = 7.9 Hz), 5.46 d (1H, 2′-H, *J* = 13.5 Hz), 6.43 d (1H, 1′-H, *J* = 13.5 Hz). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 10.70 and 11.02 ($CH_3$), 19.97 and

22.30 ($CH_2$), 29.43 and 29.58 ($CH_2$), 31.89 ($C^{5'}$), 51.33 ($OCH_3$), 89.76 ($C^{2'}$), 105.74 ($C^4$), 107.38 ($C^5$), 108.01 ($C^2$), 147.57 ($C^{3'}$), 147.75 ($C^{1'}$), 155.27 ($C^3$), 181.94 ($C^1$), 206.20 (C=O). Found, %: C 62.96; H 8.70; Cl 7.68; N 5.88. $C_{24}H_{39}ClN_2O_4$. Calculated, %: C 63.35; H 8.64; Cl 7.79; N 6.16.

**The reaction of compound IV with *N*-methylpiperazine** was carried out as described above for the reaction with pyrrolidine. From 0.30 g (0.92 mmol) of compound **IV** and 0.26 ml (3.68 mmol) of *N*-methylpiperazine we obtained 0.2 g (~50%) of compound **Vf** and 0.06 g (17%) of **VI** which were separated by column chromatography on silica gel using as eluent first ethyl acetate–petroleum ether (2:1) and then ethyl acetate.

**5-[(*Z*,2*E*)-1-Acetyl-3-(4-methylpiperazino)prop-2-en-1-ylidene]-2-chloro-4,4-dimethoxy-3-(4-methylpiperazin-1-yl)cyclopent-2-en-1-one (Vf).** Yellow–brown oily substance. $^1$H NMR spectrum, δ, ppm: 2.31 s (3H, $NCH_3$), 2.33 s (3H, $NCH_3$), 2.43 m (2H, $NCH_2$), 2.45 s (3H, $CH_3$), 2.56 m (4H, $NCH_2$), 3.19 s (6H, $OCH_3$), 3.26 m (4H, $NCH_2$), 4.08 m (6H, $NCH_2$), 5.51 d (1H, 2′-H, $J$ = 13.91 Hz), 6.35 d (1H, 1′-H, $J$ = 13.93 Hz).

**1-{(1*E*)-3-[(1*E*)-3-(2-Carboxypyrrolidin-1-yl)-4-chloro-2,2-dimethoxy-5-oxocyclopent-3-en-1-ylidene]-4-oxopent-1-en-1-yl}pyrrolidine-2-carboxylic acid (Vg)** was synthesized as described above for compound **Vc** from 0.1 g (0.3 mmol) of chloro ketone **IV** and 0.2 g (1.2 mmol) of proline. Yield 0.04 g (27%), oily substance. $^1$H NMR spectrum, δ, ppm: 2.22 m (4H, $CH_2$, $J$ = 7.3 Hz), 2.51 s (3H, $CH_3$), 2.56 t (2H, $CH_2$, $J$ = 8.1 Hz), 2.61 t (2H, $CH_2$, $J$ = 8.2 Hz), 3.24 s (6H, $OCH_3$), 3.30–3.50 m (4H, $NCH_2$), 3.67 t (1H, NCH, $J$ = 7.4 Hz), 3.75 t (1H, NCH, $J$ = 7.3 Hz), 6.19 d (1H, 2′-H, $J$ = 14.8 Hz), 7.57 d (1H, 1′-H, $J$ = 14.8 Hz).

**2,5-Dichloro-4,4-dimethoxy-5-(2-methylfuran-3-yl)-3-(4-methylpiperazin-1-yl)cyclopent-2-en-1-one (VI).** Dark yellow oily substance. $^1$H NMR spectrum, δ, ppm: 1.89 s (3H, $CH_3$), 2.39 s (3H, $NCH_3$), 2.61 m (4H, $NCH_2$), 3.18 s and 3.28 s (3H each, $OCH_3$), 4.13 m (4H, $NCH_2$), 6.08 d (1H, 4′-H, $J$ = 2.73 Hz), 7.18 d (1H, 5′-H, $J$ = 2.70 Hz).

**2,3-Dichloro-4,4-dimethoxy-5-(2-methylfuran-3-yl)cyclopent-2-en-1-one (VII).** A solution of 0.076 g (0.76 mmol) of diisopropylamine in 5 ml of anhydrous tetrahydrofuran was cooled to –78°C, and 0.6 ml (0.76 mmol) of a 1.5 N solution of butyllithium in hexane was added dropwise under stirring in an argon atmosphere. The mixture was stirred for 10 min at –78°C, the cooling bath was removed, the mixture was allowed to warm up to 0°C, stirred for 30 min, and cooled again to –78°C, and a solution of 0.2 g (0.68 mmol) of compound **IV** in 3 ml of anhydrous THF was added dropwise. The mixture was stirred for 1 h at –78°C, a solution of ammonium chloride was added dropwise, and THF was distilled off. The residue was extracted with chloroform (3×20 ml), and the organic extract was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:9) as eluent. Yield 0.10 g (66%). Colorless crystals, mp 96–98°C. $^1$H NMR spectrum, δ, ppm: 2.25 s (3H, $CH_3$), 3.34 s (3H) and 3.42 s (3H, $OCH_3$), 3.88 s (1H, 5-H), 6.14 d (1H, 4′-H, $J$ = 1.8 Hz), 7.25 d (1H, 5′-H, $J$ = 1.8 Hz). $^{13}$C NMR spectrum, $\delta_C$, ppm: 11.94 ($CH_3$), 51.38 and 51.51 ($OCH_3$), 54.74 ($C^5$), 102.49 ($C^4$), 111.53 ($C^2$), 111.35 ($C^{4'}$), 134.81 ($C^{3'}$), 140.34 ($C^{5'}$), 150.49 ($C^{2'}$), 158.49 ($C^3$), 192.14 (C=O). Found, %: C 50.03; H 4.50; Cl 23.96. $C_{12}H_{12}Cl_2O_4$. Calculated, %: C 49.51; H 4.15; Cl 24.36.

**2-Chloro-4,4-dimethoxy-5-(2-methylfuran-3-yl)-3-morpholinocyclopent-2-en-1-one (VIII)** was synthesized as described above for compound **Vc** from 0.1 g (0.34 mmol) of compound **VII** and 0.12 ml (1.36 mmol) of morpholine. Yield 0.08 g (68%). Colorless powder, mp 112–114°C. $^1$H NMR spectrum, δ, ppm: 2.26 s (3H, $CH_3$), 3.0 s and 3.35 s (3H each, $OCH_3$), 3.69 s (1H, 5-H), 3.79 m (4H, $NCH_2$), 3.97 m (4H, $OCH_2$), 6.12 d (1H, 4′-H, $J$ = 1.8 Hz), 7.22 d (1H, 5′-H, $J$ = 1.8 Hz). $^{13}$C NMR spectrum, $\delta_C$, ppm: 11.84 ($CH_3$), 47.79 ($C^5$), 48.93 ($CH_2N$), 50.96 and 51.73 ($OCH_3$), 67.19 ($CH_2O$), 104.01 ($C^4$), 106.31 ($C^2$), 111.08 ($C^{4'}$), 113.02 ($C^{3'}$), 140.23 ($C^{5'}$), 149.85 ($C^{2'}$), 159.64 ($C^3$), 190.86 ($C^1$). Found, %: C 55.90; H 6.20; Cl 9.89; N 3.86. $C_{16}H_{20}ClNO_5$. Calculated, %: C 56.23; H 5.90; Cl 10.37; N 4.10.

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