Reaction of 11-Methoxy-6,11-dihydrodibenz[*b*,*e*]oxepins with Active Methylene Compounds[1)]

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A new method for effecting the formation of a carbon–carbon single bond at the 11-position of 6,11-dihydrodibenz[*b*,*e*]oxepins was developed. The reaction of 11-methoxydibenz[*b*,*e*]oxepins with active methylene compounds proceeded in the presence of $TiCl_4$ under mild conditions to afford the corresponding 11-substituted dibenzoxepins in moderate to excellent yield. This was considered to be a vinylogous reaction of ketals with active methylene compounds. The efficacy and some applications of this method are described.

Keywords 6,11-dihydrodibenz[*b*,*e*]oxepin; 11-methoxydibenz[*b*,*e*]oxepin; bond formation; Lewis acid; active methylene compound; ethyl cyanoacetate

In the course of studies on new antithrombotic agents, we attempted to synthesize compound **1** which is a derivative of the potent thromboxane A_2 receptor antagonists **3** and **4** (see Fig. 1).[2)] Although compound **1** was expected to be obtainable from a 1,3-dicarbonyl compound **2**, dibenzoxepin derivatives of this type have not been reported. Thus we investigated the reaction of 6,11-dihydrodibenz[*b*,*e*]-oxepins with active methylene compounds. In this paper we describe a novel method for carbon–carbon single bond formation at the 11-position of the dibenzoxepin ring system.

Few examples of dibenz[*b*,*e*]oxepin derivatives possessing a carbon–carbon single bond as the connecting group at the 11-position are available in the literature, though the preparation of doxaminol (**8**), a partial β-agonist, has been reported as outlined in Chart 1.[3)]

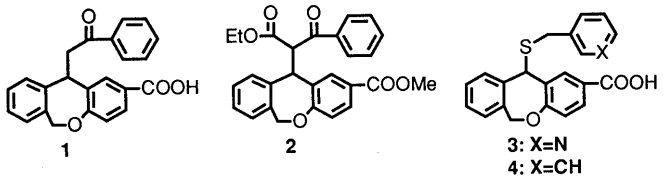


Fig. 1

Initially, we examined the reaction of the chloride **9** with diethyl malonate in the presence of a base (*e.g.*, NaH and NaOEt, method A), but the yield of **10** was low[4)] (Chart 2). Next, the Lewis acid-mediated substitution of the methoxy group at the 11-position with diethyl malonate was examined (method B), since the methoxy group in the dibenz[*b*,*e*]oxepin ring system was regarded as a vinylogue of ketals [MeO–C(11)–C(11a)=C(4a)–O(5)–C(6)].[5)] Compound **11**[6)] was found to be converted into **10** in the presence of $TiCl_4$ at room temperature in good yield,[7)] whereas compound **12** was a main poduct in the presence of $BF_3 \cdot Et_2O$.[8)] The absence of diethyl malonate did not affect the reaction to provide **12**.

Table I illustrates some applications of this method. The methoxycarbonyl-substituted derivative (**14**)[6)] was allowed to react with ethyl cyanoacetate to provide **17** in a moderate yield (entry 5). However, the reaction of **13**[6)] with ethyl cyanoacetate did not proceed upon simple treatment with $TiCl_4$ (entry 2). Addition of diisopropylethylamine modulated the reaction (entries 1 and 3). Compound **15** was obtained in a benzene solution containing 1 eq of diisopropylethylamine (entry 3). The amine might act as a

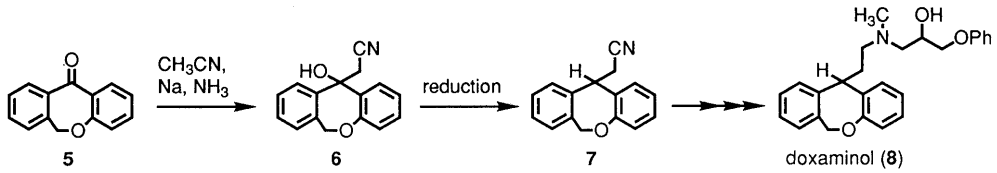


Chart 1

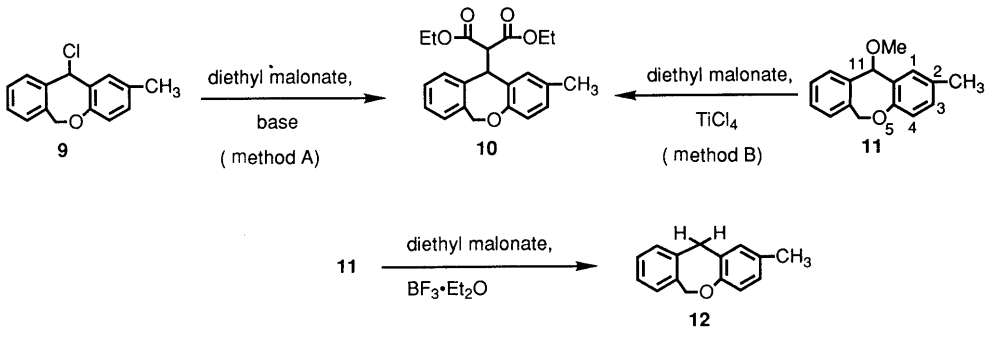
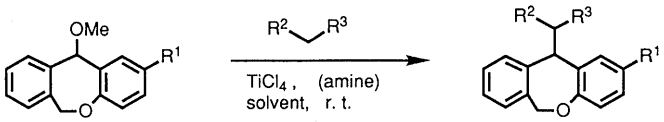
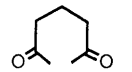


Chart 2

TABLE I. Reaction of 11-Methoxy-6,11-dihydrodibenz[*b*,*e*]oxepins with Active Methylene Compounds



Entry	Methyl ether	R^1	R^2	R^3	Product	Solvent	Amine	Time (h)	Yield[a] (%)
1	**13**	H	COOEt	CN	**15**	CH_2Cl_2	iso-Pr_2NEt	12	0[b]
2	**13**	H	COOEt	CN	**15**	Benzene	—	12	0[c]
3	**13**	H	COOEt	CN	**15**	Benzene	iso-Pr_2NEt	5	69
4	**11**	Me			**16**	Benzene	—	2	94
5	**14**	COOMe	COOEt	CN	**17**	CH_2Cl_2	—	12	48
6	**14**	COOMe	COOEt	COPh	**18**	CH_2Cl_2	—	2	96

a) Isolated yield. *b*) Starting methyl ether was recovered. *c*) Starting methyl ether was decomposed.

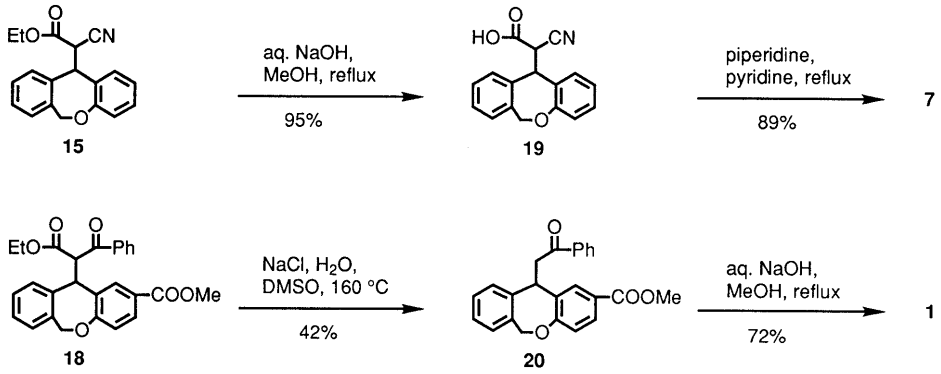


Chart 3

proton scavenger. Treatments of **11** and **14** with 1,3-cyclohexanedione and ethyl benzoylacetate afforded **16** and **18**, respectively, in excellent yields (entries 4 and 6).

Compound **15** and **18** were useful precursors of **7** and **1**, respectively, as demonstrated in Chart 3. Alkaline saponification of **15** provided **19**, which was treated with pyridine containing 1 eq of piperidine to afford **7**. Similarly, the ethoxycarbonyl group of **18** was selectively removed by heating with NaCl in wet dimethyl sulfoxide (DMSO),[9] and the subsequent hydrolysis of **20** provided **1**.

In conclusion, we have developed a new method for effecting carbon–carbon single bond formation at the 11-position of the dibenzoxepin ring system. 11-Methoxy-6,11-dihydrodibenz[*b*,*e*]oxepins underwent reaction with active methylene compounds in the presence of $TiCl_4$ at room temperature. Addition of diisopropylethylamine was effective in the case of ethyl cyanoacetate. This method should be useful for the preparation of new pharmacologically interesting dibenzoxepin derivatives. The biological activity profiles of the compounds obtained in this study will be reported separately.

Experimental

General Procedures Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Hitachi R-90H (90 MHz), or a JEOL GX-270 (270 MHz) spectrometer with Me_4Si as an internal standard. Mass spectra (MS) were recorded on a JEOL D300 mass spectrometer. Elemental analyses were performed by the analytical department of our laboratories. For column chromatography, silica gel (Kieselgel 60, Merck, 70—230 or 230—400 mesh) was used.

(2-Methyl-6,11-dihydrodibenz[*b*,*e*]oxepin-11-yl)malonic Acid Diethyl Ester (10) from the Chloride 9 (Method A) The unstable chloride **9** was prepared by the same method as described in our previous report[6] and used without purification in the next reaction. A mixture of diethyl malonate (0.3 ml, 1.98 mmol), EtONa (140 mg, 2.06 mmol), and EtOH (50 ml) was heated at 50 °C until the suspension changed into a solution, and then concentrated. The residue and chloride **9** (crude, 0.53 g, *ca.* 1.8 mmol) were suspended in benzene (50 ml), and the mixture was refluxed for 3.5 h, then diluted with EtOAc. The organic solution was washed with brine, dried, and concentrated. The crude product was chromatographed on silica gel (hexane : EtOAc = 5 : 1) to give 0.11 g (16%) of **10** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (t, J=7.0 Hz, 6H), 2.25 (s, 3H), 3.93, 3.96 (each q, J=7.0 Hz, total 4H), 4.48, 4.70 (AB-q, J=11.1 Hz, 2H), 4.99, 5.54 (AB-q, J=15.5 Hz, 2H), 6.8—7.4 (m, 7H). IR (neat): 1720 cm^{-1}. High resolution MS *m*/*z*: Calcd for $C_{22}H_{24}O_5$ 368.1624. Found 368.1634 (M^+).

From the Methyl Ether 11 (Method B) $TiCl_4$ (0.4 g, 2.1 mmol) was added to a mixture of the methyl ether **11**[6] (0.5 g, 2.1 mmol) and diethyl malonate (1.0 ml, 6.6 mmol) in benzene (1 ml) at room temperature. The mixture was stirred at room temperature for 1 h, then poured into ice-water. The crude product was extracted with EtOAc. The extract was washed with brine, dried, and evaporated, and the residue was purified by the same method as described above to give 0.7 g (91%) of **10**.[7]

(6,11-Dihydrodibenz[*b*,*e*]oxepin-11-yl)cyanoacetic Acid Ethyl Ester (15) The methyl ether **13**[6] (1.0 g, 4.4 mmol) and ethyl cyanoacetate (0.5 ml, 4.7 mmol) were dissolved in CH_2Cl_2 (50 ml, entry 1) or benzene (50 ml, entries 2 and 3). Diisopropylethylamine (0.8 ml, 4.6 mmol) was added (entries 1 and 3). A solution of $TiCl_4$ in CH_2Cl_2 (1 M, 4.5 ml, 4.5 mmol) was added and the resultant mixture was stirred at room temperature for 12 h (entries 1 and 2) or 5 h (entry 3). MeOH (5 ml) was added and the reaction mixture was diluted with CH_2Cl_2 (entry 1) or EtOAc (entries 2 and 3). The organic solution was washed with brine, dried, and evaporated. The crude product was chromatographed on silica gel (hexane : EtOAc = 6 : 1) to give 0.94 g (69%) of **15** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.98, 1.05 (each t, J=7.2 Hz, total 3H), 3.98, 4.00 (each q, J=7.2 Hz, total 2H), 4.29, 4.72 (AB-q, J=11.0 Hz, 1H), 4.32, 4.74 (AB-q, J=15.8 Hz,

2H), 5.03, 5.51 (AB-q, $J=15.8$ Hz, 2H). IR (neat): 2248, 1738 cm^{-1}. *Anal.* Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.36; H, 5.71; N, 4.31.

2-(2-Methyl-6,11-dihydrodibenz[*b,e*]oxepin-11-yl)-1,3-dioxocyclohexane (16) A solution of $TiCl_4$ (1 M, 6 ml, 6 mmol) was added to a suspension of the methyl ether **11** (1.0 g, 4.2 mmol) and 1,3-dioxocyclohexane (1.4 g, 12 mmol) in benzene (6 ml), and the mixture was stirred at room temperature for 2 h. MeOH (5 ml) was added and the solution was concentrated. The crude product was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (hexane : EtOAc = 4 : 1) to give 1.26 g (94%) of **16** as an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.5 (m, 6H), 5.12, 5.35 (AB-q, $J=14.8$ Hz, 2H), 6.30 (s, 1H), 6.8—7.3 (m, 7H), 10.08 (s, 1H). IR (KBr): 3190, 1644, 1606, 1505, 1257, 999 cm^{-1}. *Anal.* Calcd for $C_{21}H_{20}O_3$: C, 78.90; H, 6.19. Found: C, 78.73; H, 6.29.

[2-(Methoxycarbonyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-yl]cyanoacetic Acid Ethyl Ester (17) The methyl ether **14**[6] (2.7 g, 9.5 mmol) and ethyl cyanoacetate (1.0 ml, 9.5 mmol) were dissolved in CH_2Cl_2 (60 ml). A solution of $TiCl_4$ in CH_2Cl_2 (1 M, 10 ml, 10 mmol) was added, and the mixture was stirred at room temperature for 12 h. MeOH (5 ml) was added and the reaction mixture was diluted with CH_2Cl_2. The organic solution was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (hexane : EtOAc = 3 : 1) to give 1.65 g (48%) of **17** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.06, 1.08 (each t, $J=7.1$ Hz, total 3H), 3.88, 3.89 (each s, total 3H), 3.9—4.2 (m, 2H), 4.40, 4.63 (AB-q, $J=11.0$ Hz, 1H), 4.43, 4.65 (AB-q, $J=11.0$ Hz, 1H), 5.05, 5.59 (AB-q, $J=15.6$ Hz, 2H), 6.9—8.2 (m, 7H). IR (neat): 2248, 1744, 1719 cm^{-1}. MS *m/z*: 365 (M^+). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.00; H, 5.46; N, 3.64.

Compound **18**, [2-(methoxycarbonyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-yl]benzoylacetic acid ethyl ester, was prepared from **14** and ethyl benzoylacetate by a similar method to that described above (96%). **18**: An amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.94, 0.96 (each t, $J=7.1$ Hz, total 3H), 3.86, 3.88 (each s, total 3H), 3.6—4.0 (m, 2H), 4.8—5.8 (m, 4H), 6.8—8.1 (m, 12H). IR ($CHCl_3$): 1720, 1687, 1117 cm^{-1}. *Anal.* Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.87; H, 5.67.

(6,11-Dihydrodibenz[*b,e*]oxepin-11-yl)cyanoacetic Acid (19) A mixture of **15** (0.94 g, 3.06 mmol), 10 N NaOH (1.0 ml, 10 mmol), MeOH (30 ml), and water (10 ml) was refluxed for 45 min. After being cooled, the reaction mixture was concentrated and the residue was diluted with water. The medium was adjusted to pH 2 with 4 N HCl and the product was extracted with ether. The extract was dried and concentrated to give 0.81 g (95%) of **19** as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 4.29, 4.75 (AB-q, $J=10.9$ Hz, 1H), 4.32, 4.75 (AB-q, $J=11.0$ Hz, 1H), 5.03, 5.51 (AB-q, $J=15.7$ Hz, 2H), 6.85—7.55 (m, 8H). IR (neat): 2978, 2248, 1721, 1493 cm^{-1}. MS *m/z*: 279 (M^+). The crude **19** was used in the next reaction without further purification.

11-(Cyanomethyl)-6,11-dihydrodibenz[*b,e*]oxepin (7) Compound **19** (0.8 g, 2.9 mmol) was dissolved in pyridine (6 ml) containing piperidine (0.3 ml, 3.0 mmol), and the solution was refluxed for 2 h. After being cooled, the reaction mixture was diluted with EtOAc. The extract was washed with brine, dried, and concentrated. The crude product was triturated with diisopropyl ether to give 0.6 g (89%) of **7** as a powder, mp 83—84 °C (lit.[3] mp 87—89 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.17 (d, $J=7.9$ Hz, 2H), 4.10 (t, $J=7.9$ Hz, 1H), 5.01, 5.43 (AB-q, $J=15.5$ Hz, 2H), 6.85—7.55 (m, 8H). IR ($CHCl_3$): 2248, 1494, 1447, 1233 cm^{-1}. MS *m/z*: 235 (M^+). *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.65; H, 5.68; N, 5.77.

11-Phenacyl-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid Methyl Ester (20) A mixture of **18** (1.25 g, 2.9 mmol), NaCl (0.2 g, 3.4 mmol), H_2O (0.15 ml, 8.3 mmol), and DMSO (4 ml) was heated at 150—160 °C (bath temperature) for 8 h. After being cooled, the reaction mixture was diluted with ether. The organic solution was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed on silica gel (hexane : EtOAc = 2 : 1) to give 0.45 g (42%) of **20** as a yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 3.7—3.9 (m, 2H), 3.86 (s, 3H), 4.86 (t, $J=6.9$ Hz, 1H), 5.10, 5.61 (AB-q, $J=14.5$ Hz, 2H), 7.00 (d, $J=8.4$ Hz, 1H), 7.0—8.9 (m, 10H), 8.03 (d, $J=2.0$ Hz, 1H). IR (neat): 1716, 1292 cm^{-1}. MS *m/z*: 372 (M^+).

11-Phenacyl-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid (1) A mixture of **20** (0.45 g, 1.2 mmol), 10 N NaOH (1 ml, 10 mmol), MeOH (20 ml), and dioxane (20 ml) was refluxed for 6 h. Acetic acid (0.6 ml, 10 mmol) was added and the mixture was concentrated. The residue was diluted with EtOAc. The organic solution was washed with brine, dried, and concentrated. The crude product was recrystallized from MeOH to give 0.31 g (72%) of **1** as colorless crystals, mp 199—200 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.88, 3.97 (ABX, $J=6.8$, 17.3 Hz, 2H), 4.90 (t, $J=6.8$ Hz, 1H), 5.22, 5.72 (AB-q, $J=13.9$ Hz, 2H), 6.93 (d, $J=8.5$ Hz, 1H), 7.1—7.65 (m, 8H), 7.69 (dd, $J=2.1$, 8.5 Hz, 1H), 7.87 (d, $J=2.1$ Hz, 1H), 7.96 (dd, $J=1.5$, 7.1 Hz, 1H). IR (KBr): 1674, 1220, 1128 cm^{-1}. MS *m/z*: 358 (M^+). *Anal.* Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 77.17; H, 5.11.

Acknowledgement We are grateful to Mr. T. Yasuzawa, Ms. I. Hattori, and Mrs. M. Yoshida for analytical and spectral data.

References and Notes

1) Reactivity of "11-Methoxy-6,11-dihydrodibenz[*b,e*]oxepins. I."
2) Compounds **3** and **4** each inhibited the specific binding of [^{3}H]U-46619 to guinea pig platelet TXA_2 receptors with K_i values of 250 and 40 nM, respectively.
3) Brit. Patent 1129029 (1968) [*Chem. Abstr.*, **70**, 37664*r* (1969)].
4) When EtONa was used in EtOH, for example, compound **10** was obtained in a yield of 16% and the 11-ethoxycarbonylacetoxy derivative, an ester exchange product, was also observed (25%).
5) R. Antonioletti, F. Bonadies, and A. Scettri, *J. Org. Chem.*, **53**, 5540 (1988).
6) The syntheses of the chloride **9** and methyl ether **11** were reported in our previous paper. Compounds **11** (mp 52—53 °C) and **13** (oil) were prepared in a similar manner. See, E. Ohshima, T. Kumazawa, H. Takizawa, H. Harakawa, H. Sato, H. Obase, Y. Oiji, A. Ishii, H. Ishii, and K. Ohmori, *Chem. Pharm. Bull.*, **39**, 2724 (1991).
7) Since a considerable amount of diethyl malonate contaminated the product **10**, the yield could not be calculated accurately. However, TLC and ^{1}H-NMR analyses suggested that the yield of **10** was over 80%.
8) While compound **12** was produced by hydride transfer to the cation generated at the 11-position, the source of hydride was uncertain. Compound **12**: A colorless syrup. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (s, 3H), 4.18 (s, 2H), 5.26 (s, 2H), 6.7—7.5 (m, 7H). MS *m/z*: 210 (M^+). *Anal.* Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.57; H, 6.88.
9) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, **1973**, 957.