Synthesis of Polysubstituted Dioxoles from the Cycloaddition of Diazo Dicarbonyl Compounds to Aldehydes and Ketones under Copper(II) Catalysis†

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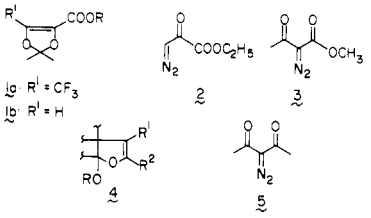
The copper(II) chelate catalyzed addition of compounds 2-diazo-3-oxobutyrate (**3**) and 3-diazo-2,4-pentanedione (**5**) in the presence of aldehydes and ketones in refluxing aromatic solvents proceeds smoothly with the exclusive formation of dioxole derivatives. The yield of 1:1 adducts depends strongly on the nature of the copper ligands and relative concentration of catalyst employed. Dioxoles are the only volatile materials present within a 2% detection limit. The general character of this novel cycloaddition is illustrated with the reaction of **3** and **5** with four aldehydes and nine ketone substrates.

The most incisive information concerning the chemical characteristics of diazocarbonyl compounds comes from extensive studies of addition reactions involving the carbon–carbon multiple bond.[1] Less well-known are those additions that entail carbon–heteroatom multiple linkages.[2] Of these, the less well understood are the reactions with carbonyl systems, in spite of their having been first explored a century ago.[3] An impediment to the development of diazo carbonyl additions to carbonyl is, no doubt, the complexity of the process by which the two systems interact.[4-8]

Exceptional among this prior art was the report of the unexpected, photolytically induced cycloaddition of alkyl 2-diazo-4–trifluoroacetoacetate to acetone, whereby dioxole **1** was obtained among other products.[9] The possibility that this cycloaddition had occurred by way of a 1,3-dipolar coupling offered a feasible synthetic entry to these little known heterocycles by using other diazo carbonyl compounds with proved potential toward 3 + 2 cycloaddition in reactions with carbon–carbon multiple bonds. Recently, this hypothesis has been realized in this laboratory with ethyl diazopyruvate (**2**) and methyl 2-diazo-3-oxobutyrate (**3**).[10] These results, which appeared in prelimianry form[11] have been expanded to a greater extent. These developments are reported in the present work.

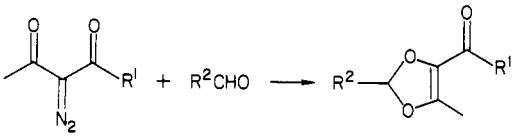


Results and Discussion

Some diazo dicarbonyl compounds studied in this laboratory display a remarkable tendency toward 1,3-dipolar addition during their transition metal catalyzed decomposition in the presence of electron rich olefins, as opposed to their monocarbonyl counterparts.[10] This quality, studied in the present case with alkyl 2-diazo-3-oxobutyrate (**3**) and 3-diazo-2,4-pentanedione (**5**) is also reflected in the exclusive formation of dioxoles from their interaction with aldehydes and ketones of various substitution patterns, under copper(II) catalysis.

Thus, the reaction of compound **5** with aldehydes (Table I), produced 3-acyl-4-methyl-2-alkyldioxoles as the only volatile products in moderate to high yield, in parallel with the reactions of compounds **2** and **3** with aldehydes studied

Table I. Reactions of Compounds 3 and 5 with Aldehydes[a]



6a-d

entry	R^1	R^2	product	yield, %
1	OCH_3	$(CH_3)_2CH$	**6a**	80
2	CH_3	$(CH_3)_2CH$	**6b**	70
3	CH_3	2-furoyl	**6c**	52
4	CH_3	$CH_3CH{=}CH$-*t*	**6d**	49

[a] Under conditions of maximum yield. See Table IV.

† Contribution No. 3314.

(1) Kirmse, W. "Carbene Chemistry", 2nd ed.; Academic Press: New York, 1971. Moss, R. A. *Sel. Org. Transform.* **1969**, *1*, 35. Marchand, A. P.; Brockway, N. M. *Chem. Rev.* **1974**, *74*, 431. Moss, R. A., Jones, M., Jr., Eds. "Carbenes"; Wiley-Interscience: New York, 1975; Vol. I and II. Patai, S., Ed. "The Chemistry of Diazo and Diazonium Groups"; Wiley-Interscience: New York, 1978; Parts I and II.

(2) The most extensively studied case is that where nitriles act as substrates. Oxazoles systematically result. See: Huisgen, R. *Angew. Chem., Int. Ed. Eng.* **1963**, *2*, 565, 633. Huisgen, R.; Sturm, H. L.; Binsch, G. *Chem. Ber.* **1964**, *97*, 2864. Huisgen, R.; Binsch, G.; Ghosez, L. *Ibid.* **1964**, *97*, 2628. Huisgen, R.; Blaschke, H. *Liebigs Ann. Chem* **1965**, *696*, 145. Buu, N. T.; Edward, J. T. *Can. J. Chem.* **1972**, *50*, 3730. Dworschak, H.; Weygand, F. *Chem. Ber.* **1968**, *101*, 302. Kitatani, K.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1974**, 1531. Paulissen, R.; Moniotte, Ph.; Hubert, A. J.; Teyssie, Ph. *Tetrahedron Lett.* **1974**, 3311. Moniotte, Ph.; Hubert, A. J.; Teyssie, Ph. *J. Organometal. Chem.* **1975**, *88*, 115. Lakhan, R.; Turnai, B. Adv. *Heterocycl. Chem.* **1974**, *17*, 99. Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Japan* **1977**, *50*, 1647. Ibata, T.; Sato, R. *Ibid.* **1979**, *52*, 3597. Flowers, T. W.; Holt, G.; McCleery, P. P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1485. Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657.

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(5) Gutsche, C. D. *Org. React.* **1954**, *8*, 364. Marshall, J. A.; Partridge, J. J. *Tetrahedron* **1969**, *25*, 2155. Wasfi, A. S. *J. Indian Chem. Soc.* **1970**, *47*, 341. Liu, H. J. *Majumdar*, S. P. *Synth. Commun.* **1975**, *5*, 125. Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459 and 466. Baldwin, S. W.; Doll, R. J. *Tetrahedron Lett.* **1979**, 3275. Loeschorn, C. A.; Nakajima, M.; McCloskey, P. J.; Anselme, J.-P. *J. Org. Chem.* **1983**, *48*, 4407. The homologation of acetals of α,β-unsaturated carbonyls also has been reported recently. See: Doyle, M. P.; Trudell, M. L.; Terpstra, J. W. *J. Org. Chem.* **1983**, *48*, 5146.

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(7) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952 and 4953 and references cited therein.

(8) Landgrebe, J. A.; Iranmanesh, H. *J. Org. Chem.* **1978**, *43*, 1244.

(9) Dworschak, H.; Weygand, F. *Chem. Ber.* **1968**, *101*, 289.

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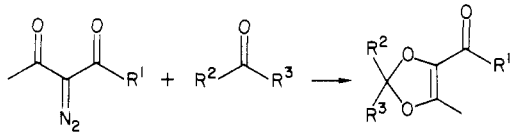
Table II. Products and Yields of the Reaction of Compounds 3 and 5[a] with Acyclic Ketones

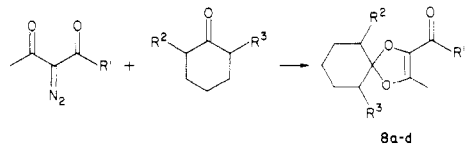


7a-l

entry	R^1	R^2	R^3	product	yield, %
1	OCH_2CH_3	CH_3	CH_3	**7a**	74
2	CH_3	CH_3	CH_3	**7b**	45
3	OCH_3	$(CH_3)_2CH$	CH_3	**7c**	77
4	CH_3	$(CH_3)_2CH$	CH_3	**7d**	51
5	OCH_3	$(CH_3)_2CHCH_2$	CH_3	**7e**	65
6	CH_3	$(CH_3)_2CHCH_2$	CH_3	**7f**	27
7	OCH_3	CH_3CH_2	CH_3CH_2	**7g**	42
8	CH_3	CH_3CH_2	CH_3CH_2	**7h**	26
9	OCH_3	$(CH_3)_2CH$	$(CH_3)_2CH$	**7i**	25
10	CH_3	$(CH_3)_2CH$	$(CH_3)_2CH$	**7j**	17
11	OCH_3	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	**7k**	42
12	CH_3	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	**7l**	31

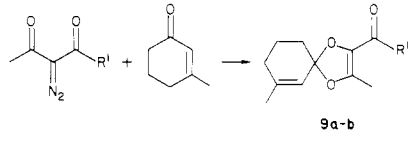
[a] Under conditions of maximum yield. See Table IV.

Table III. Products and Yields for the Reaction of Compounds 3 and 5[a] with Alicyclic Ketones



8a-d

entry	R^1	R^2	R^3	product	yield, %
1	OCH_3	H	H	**8a**	64
2	CH_3	H	H	**8b**	64
3	OCH_3	CH_3	CH_3	**8c**	18
4	CH_3	CH_3	CH_3	**8d**	18



9a-b

5	OCH_3			**9a**	45
6	CH_3			**9b**	38

[a] Under conditions of maximum yield. See Table IV.

earlier.[11] The nonvolatile fraction consisted of intractable polymeric material.

The reaction of compounds **3** and **5** with ketones was also examined. Their addition to nine different ketones under a variety of experimental conditions gave only the corresponding dioxole derivatives (Tables II and III), in yields ranging from 17 to 77%. A rough correlation between steric encumbrance of the substrate ketone and yield was observed with both **3** and **5**. For example, branching of the starting ketone at one of the α carbons did not change appreciably the yield of dioxole. However, substitution at both α carbons caused a marked decrease in yield of heterocycle. α substitution had a greater bearing on yield of dioxole than β branching as indicated by the

Table IV. Relationship between Ligands of Metal Catalyst and Yield of Adducts 6a and 6b, Obtained from Diazo Compounds 3 and 5, Respectively, and Isopropanaldehyde in Benzene at 80 °C, 3 mol % Catalyst in Relation to Diazo Compound

entry	catalyst[a]	% **6a**	reaction time, h	% **6b**	reaction time, h
1	a	75	4.5	27	48
2	b	56	26	44	23
3	c	14	23		72
4	d	77	15	52	27
5	e	80	5	70	0.5
6	f	61	5.5	54	22
7	g		48		48

[a] a, bis(ethyl acetoacetate)copper(II); b, bis(benzoylacetonato)-copper(II); c, bis(acetoacetonato)copper(II); d, bis(trifluoroacetoacetonato)copper(II); e, bis(hexafluoroacetoacetonato)copper(II); f, copper(II) triflate; g, $(C_6H_5)_3P{\cdot}CuI$.

reactions of **3** and **5** with 2,4-dimethyl-3-pentanone and 2,6-dimethyl-4-heptanone.

Similar results were observed in the cyclic ketone series, (Table III) in which 2,6-dimethylcyclohexanone gave the poorest recovery yield. This is consistent with the generally higher yields obtained for the aldehyde series. In no case were other tractable products detected in crude reaction mixtures. The absence of more complex products is probably due to the relatively low concentration of carbonyl reactant at all times in the reaction course (see Experimental Section). Considerable latitude on the structure of the resulting dioxoles, therefore, is achieved with diazo compounds **2**, **3**, and **5**, for di-, and tri-, and tetrasubstituted heterocycles are obtained. The carbonyl unit on C-3 provides additional opportunity for versatile functionalization.

Of some interest is the fact that α,β-unsaturated aldehydes and ketones gave only the corresponding dioxoles without migration of the double bond as opposed to the construction of dioxolanes from enones.[12,13] This fact suggests either a synchronous 1,3-dipolar cycloaddition of the putative copper ketocarbenoid[14] to the C=O bond or a very short lived ylide intermediate. Also, the regiospecific reaction on the carbonyl group may be explained by the low electron density of the C=C bond which decreases its reactivity toward the electrophilic carbenoid.

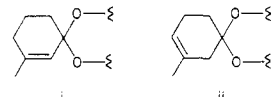
The yield of dioxole is strongly dependent on the nature of ligands of the metal catalyst and oxidation state of

(10) Wenkert, E. *Heterocycles* **1980**, *14*, 1703 and references cited. Alonso, M. E.; Morales, A.; Chitty, A. W. *J. Org. Chem.* **1982**, *47*, 3747. Alonso, M. E.; Jano, P.; Hernández, M. I.; Greenberg, R. S.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 3047. Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Sánchez, E. L. *J. Am. Chem. Soc.* **1983**, *105*, 2021.

(11) (a) Alonso, M. E.; Jano, P. *J. Heterocycl. Chem.* **1980**, *17*, 721. (b) Alonso, M. E.; Chitty, A. W. *Tetrahedron Lett.* **1981**, *22*, 4184.

(12) Becker, D.; Brodsky, N. C.; Kalo, J. *J. Org. Chem.* **1978**, *43*, 2557.

(13) The position of the double bond was secured on the basis of the NMR spectrum as indicated below. The methyl group on C1 of the cyclohexenyl ring was used as a tag to distinguish either i or ii. The NMR spectrum of the isolated compound **9a** or **9b** showed a multiplet at 5.55 ppm attributable to a vinyl proton. Since i or ii would have shown similar signals on a 90 MHz spectrum, additional data was required for structural assignment. Thus, the vinyl methyl signal at 1.73 ppm was irradiated (0.2 G) and this caused the collapse of the 5.55 ppm multiplet into a singlet. Additional vicinal coupling would have remained in the vinyl proton of structure ii, and therefore it was discarded.



i ii

(14) Among other Lewis acids, copper(II) triflate has been found to be a more effective catalyst in promoting the decomposition of diazocarbonyl compounds.[15] The relatively lower yields of dioxole adduct obtained in the copper triflate decomposition of **3** and **5**, therefore, casts some doubt as to the role of other copper(II) chelates as Lewis acids in promoting their cycloaddition. Metal carbenoids are likely to be involved instead.

(15) Doyle, M. P.; Trudell, M. L. *J. Org. Chem.* **1984**, *49*, 1196.

(16) This is consistent with past experience in other diazocompound–olefin–catalyst systems. See, inter alia: Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059.

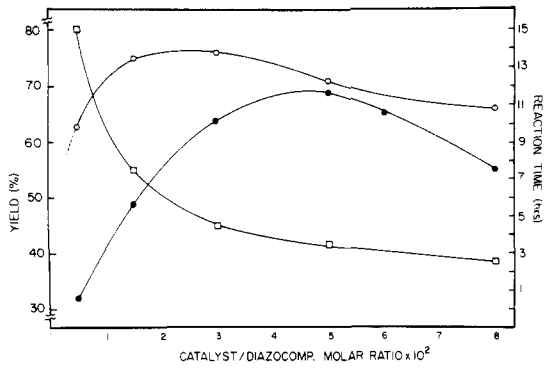


Figure 1. Effect of catalyst to diazo compound molar ratio on yield of dioxole adduct (**6**) and reaction time for the cycloaddition of **3** and **5** to isobutyraldehyde. (○): Yield of compound **6a** vs. molar ratio of bis(ethyl acetoacetate)copper(II) and compound **3**. (●): Yield of compound **6b** vs. molar ratio of bis(hexafluoroacetoacetonato)copper(II) and compound **5**. (□): Reaction time for complete decomposition of diazo ester **3** vs. catalyst/diazo compound molar ratio, in the presence of a 6-fold molar excess of isobutyraldehyde in benzene, at reflux temperature; catalyst, bis(ethyl acetoacetate)copper(II).

Table V. Effect of Solvent Polarity on Yield of Compounds 6a and 6b, Obtained from Diazo Compounds 3 and 5, Respectively, and Isopropanaldehyde with Bis(ethyl acetoacetate)copper(II) with 3 and Bis(hexafluoroacetoacetonato)copper(II) with 5

entry	solvent	T, °C	% 6a	reaction time, h	% 6b	reaction time, h
1	cyclohexane	80	33	22	46	20
2	benzene	80	75	4.5	70	5.5
3	chloro-benzene	130		24	30	4
4	fluorobenzene	80	74	4.5	69	5

copper (Table IV). This also varies markedly with the particular diazo compound used. For instance, while both **3** and **5** were found to perform best with bis(hexafluoroacetoacetonato)copper(II) in their model reaction with isobutyraldehyde, compound **5** failed to decompose to a significant extent with bis(acetoacetonato)copper(II). Yet, **3** yielded 15% of dioxole derivative with the latter catalyst. No apparent correlation between ligand strength and yield or relative steric hindrance on the part of these ligands could be found in these results.

The catalyst to diazo compound molar ratio was observed to be of importance (see Figure 1) in determining the yield of dioxole produced.[15] For compound **3** the maximum yield was obtained at 3% molar ratio, whereas this value was achieved at 5% molar ratio for compound **5**. The position of this maximum did not change appreciably with the type of catalyst used. Further, the rate of decomposition of the diazo compound changed exponentially with relatively minor variations of catalyst:diazo carbonyl proportion, particularly in the range 0.5–3%. The results appear collected in Figure 1.

Finally, the best results were obtained with benzene and fluorobenzene as solvents at their respective boiling points, as Table V indicates. Efforts to understand the mechanistic implications of this reaction continue in our laboratories.

Experimental Section

Infrared spectra were measured on a Perkin-Elmer 567 spectrophotometer in sodium chloride cells. NMR spectra were obtained with a Varian EM-390 spectrometer operating at 90 MHz, with tetramethylsilane as internal standard, and in deuteriochloroform solutions. Electron impact mass spectra were obtained with a DuPont spectrometer, Model 21-492, and exact masses were measured with a AEI-Kratos MS-30 double beam instrument. 3-Diazo-2,4-pentanedione and methyl 2-diazo-3-oxobutyrate were synthesized from acetylacetone, methyl oxobutyrate, and tosyl azide as previously described.[16] Boiling points are uncorrected. Yields were calculated based on amount of diazo carbonyl compound employed. Dioxoles obtained from diazo compounds **2**, **3**, and **5** were found to be considerably sensitive to moisture or traces of acid like that contained in long stored chloroform. The presence of carbonyl substituents on C-3 increased this reactivity. This caused inconsistency in some of the elemental analysis performed. Exact masses were determined in lieu of analyses in these cases.

General Method for the Addition of Diazo Carbonyl Compounds to Aldehydes and Ketones. A mixture of freshly distilled diazo carbonyl compound (10 mmol) and the carbonyl substrate (60 mmol) in dry benzene (30 mL) was added dropwise with vigorous magnetic stirring to a suspension of the copper catalyst (3–10 mol %) in dry benzene (2 mL) containing some carbonyl substrate (5 mmol) at reflux temperature and under a nitrogen atmosphere. After addition was complete, the mixture was tested for presence of diazo compound by means of its infrared band at 2150 cm^{-1}. Usually, heating was extended for an additional 0.5–3 h until complete decomposition. The mixture was then ice-cooled and passed through a short column of neutral alumina (activity III) or extracted with 3% aqueous potassium cyanide to separate organic material from catalyst. Solvents were evaporated in vacuo and the residue was examined by NMR spectroscopy and gas-liquid chromatography. Then, the residue was distilled at reduced pressure to obtain the purified volatile compounds. The nonvolatile residue was examined chromatographically for other heavier components.

1-(Methoxycarbonyl)-2-methyl-4-isopropyl-3,5-dioxacyclopent-1-ene (6a). From diazo ester **3** (1.6 g) and isobutyraldehyde (4.5 g), using bis(hexafluoroacetoacetonato)copper(II) (5 mol %), compound **6a** was obtained as a slightly yellowish oil (1.7 g, 80%); in one experiment 91% yield of dioxole **6a** was obtained, but the most consistent yield was in the low eighties: bp 50–53 °C (0.2 torr); IR (neat) 1730 (s, C=O), 1670 (s, C=C), 1440 (s), 1365 (s), 1250 (s, COOR), 1095 (s), 1040 (s), 755 (s) cm^{-1}; NMR δ 1.00 (d, 6 H, J = 6.0 Hz, $(CH_3)_2CH$), 2.17 (s, 3 H, CH_3C=), 3.80 (s, 3 H, COOMe), 5.63 (d, 1 H, J = 3.0 Hz, anomeric proton). Anal. Calcd for $C_9H_{14}O_4$: C, 58.04; H, 7.58; O, 34.38. Found: C, 58.11; H, 7.62; O, 34.27.

1-Acyl-2-methyl-4-isopropyl-3,5-dioxacyclopent-1-ene (6b). From diazo ketone **5** (1.9 g) and isobutyraldehyde (3.0 g) by using bis(hexafluoroacetoacetonato)copper(II) (3 mol%), compound **6b** was obtained as a yellowish oil (0.930 g, 69%): bp 62 °C (2 torr); IR (neat) 1690 (s, C=CC=O), 1630 (s, C=C), 1250 (s), 1120 (s), 1080 (s), 960 (m), 750 (m), 720 (s), 690 (s) cm^{-1}; NMR δ 0.95 (d, 6 H, J = 6.0 Hz, $(CH_3)_2CH$), 1.83–2.37 (m, 1 H, isopropyl methyne), 2.20 (s, 6 H, CH_3C= and CH_3C=O), 5.60 (d, 1 H, J = 3.0 Hz, anomeric proton) ppm; mass spectrum, m/e (%) 170 (M^+, 17), 127 (51), 99), 55 (16), 43 (100); exact mass calcd for $C_9H_{14}O_3$ m/e 170.0943, found 170.0950.

2-Acyl-3-methyl-5-(2-furoyl)-3,5-dioxacyclopent-1-ene (6c). From diazo ketone **5** (2.0 g) and furfural (8.0 g), compound **6c** was obtained as a yellow oil (1.614 g, 52%): bp 100–105 °C (0.5 torr); IR (neat) 1690 (s, C=O), 1610 (s, C=C), 1360 (s), 1240 (s), 1110 (s), 1000 (s), 920–950 (s), 730 (m), 685 (m) cm^{-1}; NMR (CCl_4) δ 2.25 (s, 6 H, CH_3C= and acyl), 6.42 (dd, 1 H, J_1 = 3.3 Hz, J_2 = 1.8 Hz, H at C-4 of furan ring), 6.60 (dd, 1 H, J_1 = 0.9 Hz, J_2 = 3.3 Hz, H at C-3 of furan ring), 6.70 (s, 1 H, anomeric proton), 7.50 (dd, 1 H, J_1 = 0.9 Hz, J_2 = 1.8 Hz); mass spectrum, m/e (%) 194 (M^+, 16), 152 (3), 43 (100); exact mass calcd for $C_{10}H_{10}O_4$ m/e 194.0579, found 194.0586.

1-Acyl-2-methyl-4-(1-propenyl)-3,5-dioxacyclopent-1-ene (6d). From diazo ketone **5** (1.5 g) and crotonaldehyde (5.5 g), compound **6d** was obtained (0.990 g, 49%) as a yellowish oil: bp 75–78 °C (2.2 torr); IR (neat) 1690 (s, C=O), 1600 (s, C=C), 1355 (s), 1240 (s), 1140–1110 (s), 940 (s), 900 (s), 730 (m) cm^{-1}; NMR δ 1.80 (d, 3 H, J = 6.0 Hz, methyl of 1-propenyl chain), 2.18 (s, 3 H, CH_3C=), 2.20 (s, 3 H, CH_3C=O), 5.64 (ddq, 1 H, J_1 = 3.0 Hz, J_2 = 6.5 Hz, J_3 = 15.5 Hz, H at C-1 of 1-propenyl chain), 6.07 (dq, 1 H, J_1 = 6.0 Hz, J_2 = 15.5 Hz, H at C-2 of 1-propenyl chain), 6.10 (d, 1 H, J = 6.5 Hz, anomeric proton); mass spectrum, m/e (%) 168 (M^+, 15), 84 (34), 43 (100); exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0790.

1-(Ethoxycarbonyl)-2,4,4-trimethyl-3,5-dioxacyclopent-1-ene (7a). From ethyl 2-diazo-3-oxobutyrate (1.6 g) and acetone (4.0 g), compound **7a** was obtained as a colorless oil (1.382 g, 74%): bp 45–46 °C 0.2 torr); IR (neat) 1730 (s, C=O), 1680 (s, C=C), 1390 (s), 1340 (s), 1285 (s), 1190 (s), 1120 (s), 1070 (m), 980 (m), 800 (m), 755 (m) cm^{-1}; NMR (CCl_4) δ 1.27 (t, 3 H, J = 6.5 Hz, $COOCH_2CH_3$), 1.51 (s, 6 H, *gem*-dimethyl), 2.10 (s, 3 H, CH_3C=), 4.17 (q, 2 H, J = 6.5 Hz, $COOCH_2CH_3$). Anal. Calcd for $C_9H_{14}O_4$: C, 58.04; H, 7.58; O, 34.38. Found: C, 58.00; H, 7.51; O, 34.49.

1-Acyl-2,4,4-trimethyl-3,5-dioxacyclopent-1-ene (7b). From diazo ketone **5** (1.5 g) and acetone (6.0 g), compound **7b** was obtained in pure form after distillation (0.842 g, 45%): bp 32 °C (0.6 torr); IR (neat) 1690 (s, C=O), 1620 (s, C=C), 1390 (s), 1300 (s), 1240 (s), 1150 (s), 1120 (s), 1080 (s), 1040 (s), 1010 (s), 920 (s), 740 (s), 620 (s) cm^{-1}; NMR δ 1.57 (s, 6 H, *gem*-dimethyl), 2.20 (s, 3 H, CH_3C=); mass spectrum, m/e (%) 156 (M^+, 24), 141 (20), 55 (17), 43 (100); exact mass calcd for $C_8H_{12}O_3$ 156.0786, found 156.0791.

1-(Methoxycarbonyl)-2,4-dimethyl-4-(2-propyl)-3,5-dioxacyclopent-1-ene (7c). From diazo ester **3** (1.0 g) and 3-meethyl-2-butanone (4.5 g), compound **7c** was obtained in pure form after distillation (1.083 g, 77%): bp 47–48 °C (0.15 torr); IR (neat) 1725 (s, C=O), 1680 (s, C=C), 1450 (s), 1390 (s), 1360 (s), 1280 (s), 1180 (s), 1120 (s), 945 (m), 850 (m), 800 (m), 750 (m) cm^{-1}; NMR δ 0.98 (d, 3 H, J = 6.0 Hz, $(CH_3)_2CH$), 1.39 (s, 3 H, $CH_3CR(O)_2$) 2.0 (sept, 1 H, J = 6.0 Hz, methyne), 2.11 (s, 3 H, CH_3C=), 3.80 (s, 3 H, COOMe). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.97; H, 8.06; O, 31.97. Found: C, 60.02; H, 8.10; 0, 31.88.

1-Acyl-2,4-dimethyl-4-(2-propyl)-3,5-dioxacyclopent-1-ene (7d). From diazo ketone **5** (1.5 g) and 3-methyl-2-butanone (5.0 g), compound **7d** was obtained in pure form after distillation (1.130 g, 51%): bp 42–43 °C (0.1 torr); IR (neat) 1690 (s, C=O), 1630 (s, C=C), 1410 (s), 1320 (s), 1270 (s), 1170 (s), 1112 (m), 1090 (m), 940 (s), 800 (m), 620 (s) cm^{-1}; NMR (CCl_4) δ 1.02 (d, 6 H, J = 6.0 Hz, $(CH_3)_2CH$), 1.45 (s, 3 H, $CH_3CR(O)_2$), 2.10 (sept, 1 H, J = 6.0 Hz, methyne), 2.22 (s, 6 H, CH_3C=O and CH_3C=C); mass spectrum, m/e (%) 184 (M^+, 9), 141 (50), 55 (12), 43 (100); exact mass calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1106.

1-(Methoxycarbonyl)-2,4-dimethyl-4-isobutyl-3,5-dioxacyclopent-1-ene (7e). From diazo ester **3** (0.800 g) and 4-methyl-2-pentanone (3.9 g), compound **7e** was obtained in pure form upon distillation (0.781 g, 65%): bp 59–60 °C (0.3 torr); IR (neat) 1725 (s, C=O), 1680 (s, C=C), 1450 (s), 1390 (s), 1280 (s), 1180 (s), 1120 (s), 945 (m), 850 (m), 750 (m) cm^{-1}; NMR δ 0.97 (d, 6 H, J = 6.0 Hz, $(CH_3)_2CH$), 1.47 (s, 3 H, $CH_3CR(O)_2$), 1.71 (d, 2 H, J = 6.0 Hz, methylene), 1.95 (m, 1 H, methyne), 2.12 (s, 3 H, CH_3C=C), 3.71 (s, 3 H, COOMe). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.65; H, 8.47; O, 29.88. Found: C, 61.61; H, 8.41; O, 29.98.

1-Acyl-2,4-dimethyl-4-isobutyl-3,5-dioxacyclopent-1-ene (7f). From diazo ketone **5** (2.0 g) and 4-methyl-2-pentanone (7.5 g), compound **7f** was obtained in pure form after distillation as a yellowish oil (0.851 g, 27%): bp 45 °C (0.03 torr); IR (neat) 1690 (s, C=O), 1620 (s, C=C), 1360 (s), 1290 (s), 1240 (s), 1190 (s), 1160 (s), 1100 (s), 940 (s), 860 (m), 790 (m) cm^{-1}; NMR δ (CCl_4) 0.97 (d, 6 H, J = 6.0 Hz, $CH_3)_2CH$), 1.50, (s, 3 H, $CH_3CRC(O)_2$), 1.75 (d, 2 H, J = 6.0 Hz, methylene), 1.96 (m, 1 H, methyne), 2.20 (s, 6 H, CH_3C=C, and CH_3C=O); mass spectrum, m/e (%) 198 (M^+, 11%), 183 (5), 141 (50), 55 (14), 43 (100); exact mass calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1255.

1-(Methoxycarbonyl)-2-methyl-4,4-diethyl-3,5-dioxacyclopent-1-ene (7g). From diazo ester **3** (1.5 g) and 3-pentanone (4.3 g), compound **7g** was obtained in pure form on distillation as a slightly yellowish oil (0.876 g, 42%): bp 57–58 °C (0.2 torr); IR (neat) 1720 (s, C=O), 1680 (s, C=C), 1445 (s), 1320 (s), 1270 (s), 1200 (s), 1130 (s), 950 (m), 760 (m) cm^{-1}; NMR δ 0.95 (t, 6 H, J = 6.5 Hz, 2 × CH_3CH_2, 1.81 (q, 4 H, J = 6.5 Hz, 2 × CH_2), 2.18 (s, 3 H), CH_3C=), 3.78 (s, 3 H, COOMe). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.97; H, 8.06, O 31.97. Found: C, 60.00; H, 8.09, 31.91.

1-Acyl-2-methyl-4,4-diethyl-3,5-dioxacyclopent-1-ene (7h). From diazo ketone **5** (1.5 g) and 3-pentanone (5.0 g), compound **7h** was obtained in pure form upon distillation as a yellowish oil (0.581 g, 26%): bp 46–48 °C (0.25 torr); IR (neat) 1690 (s, C=O), 1620 (s, C=C), 1460 (s), 1360 (s), 1290 (s), 1195 (s), 1110 (s), 990 (s), 930 (s), 850 (m), 810 (s) cm^{-1}; NMR (CCl_4) δ 0.97 (t, 6 H, J = 6.5 Hz, 2 × CH_3CH_2), 1.82 (q, 4 H, J = 6.5 Hz, 2 × CH_2), 2.22 (s, 6 H, CH_3C=C and CH_3C=O); mass spectrum, m/e (%) 184 (M^+, 19), 155 (58), 55 (17), 43 (100); exact mass calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1109.

1-(Methoxycarbonyl)-2-methyl-4,4-di-2-propyl-3,5-dioxacyclopent-1-ene (7i). From diazo ester **3** (2.0 g) and 2,4-dimethyl-3-pentanone (8.0 g), compound **7i** was obtained in pure form after two fractional distillations under vacuum as a slightly yellowish oil (0.541 g, 25%): bp 59–62 °C (0.15 torr); IR (neat) 1725 (s, C=O), 1680 (s, C=C), 1445 (s), 1305 (s), 1270 (s), 1200 (s), 1130 (s), 1110 (s), 1030 (s), 755 (m) cm^{-1}; NMR δ 0.96 (2 × d, 12 H, J = 6.0 Hz, 2 × $(CH_3)_2CH$), 2.10 (s, 3 H, CH_3C=), 3.70 (s, 3 H, COOMe). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.12; H, 8.94; O, 28.05. Found: C, 63.09; H, 9.01; O, 27.90.

1-Acyl-2-methyl-4,4-di-2-propyl-3,5-dioxacyclopent-1-ene (7j). From diazo ketone **5** (2.5 g) and 2,4-dimethyl-3-pentanone (10 g), compound **7j** was obtained upon fractional distillation in vacuo (0.719 g, 17%): bp 78–80 °C (1.0 torr); IR (neat 1690 (s, C=O), 1630 (s, C=C), 1390 (s), 1260 (s), 1170 (s), 1095 (s), 1060 (s), 975 (s), 925 (s), 790 (m), 760 (m), 620 (s), cm^{-1}; NMR δ 0.95 (2 × d, 12 H, J = 6.0 Hz, 2 × $(CH_3)_2CH$), 2.17 (s, 3 H, CH_3C=), 2.20 (s, 3 H, CH_3C=O); mass spectrum, m/e (%) 212 (M^+, 4), 169 (38), 154 (4), 55 (11), 43 (100); exact mass calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1404.

1-(Methoxycarbonyl)-2-methyl-4,4-diisobutyl-3,5-dioxacyclopent-1-ene (7k). From diazo ester **3** (1.0 g) and 2,6-dimethyl-4-heptanone (6.9 g), compound **7k** was obtained in pure form after fractional distillation as a yellowish oil (0.710 g, 42%): bp 80–82 °C (0.05 torr); IR (neat) 1730 (s), 1690 (s), 1450 (s), 1360 (s), 1280 (s) cm^{-1}; NMR δ 0.92 (d, 12 H, J = 6.0 Hz, 2 × $(CH_3)_2CH$), 1.64 (d, 4 H, methylenes), 2.10 (s, 3 H, CH_3C=), 3.70 (s, 3 H, COOMe); mass spectrum, m/e (%) 256 (M^+, 2), 200 (25), 158 (19), 86 (18), 84 (28), 70 (11), 57 (26), 43 (100); exact mass calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1683.

1-Acyl-2-methyl-4,4-diisobutyl-3,5-dioxacyclopent-1-ene (7l). From diazo ketone **5** (1.5 g) and 2,6-dimethyl-4-heptanone (7.0 g), compound **71** was obtained (0.896 g, 31%) as a yellowish oil: bp 73–74 °C (0.3 torr); IR (neat) 1690 (s, C=O), 1640 (s, C=C), 1475 (s), 1440 (s), 1380 (s), 1280 (s), 1205 (s), 1180 (m), 1130 (m), 1100 (m), 1030 (s), 940 (s), 785 (m) cm^{-1}; NMR δ 0.97 (d, 12 H, J = 6.0 Hz, 2 × $(CH_3)_2CH$), 1.75 (d, 4 H, J = 6.0 Hz, 2 × $(CH_3)_2CH$), 1.75 (d, 4 H, J = 6.0 Hz, methylenes), 2.20 (s, 6 H), CH_3C= and CH_3C=O); mass spectrum, m/e (%) 240 (M^+, 10), 225 (3), 183 (34), 55 (15), 43 (100); exact mass calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1717.

3-(Methoxycarbonyl)-4-methyl-$\Delta^{3,4}$-2,5-dioxaspiro[5,4]decane (8a). From diazo ester **3** (1.5 g) and cyclohexanone (7.0 g), compound **8a** was obtained as a colorless oil (1.50 g, 64%): bp 90–91 °C (0.2 torr); IR (neat) 1720 (s, C=O), 1680 (s, C=C), 1450 (s), 1360 (s), 1280 (m), 1250 (s), 1160 (s), 1115 (s) cm^{-1}; mass spectrum, m/e (%) 212 (M^+, 6), 169 (29), 157 (20), 98 (19), 81 (11), 70 (10), 69 (15), 55 (61), 43 (100); exact mass calcd for $C_{11}H_{16}O_4$ 212.1048, found 212.1042.

3-Acyl-4-methyl-$\Delta^{3,4}$-2,5-dioxaspiro[5,4]decane (8b). From diazo ketone **5** (1.5 g) and cyclohexanone (6.5 g), compound **8b** was obtained as a slightly yellowish oil (1.510 g, 64%): bp 93–94 °C (2.5 torr); IR (neat) 1690 (s, C=O), 1620 (s, C=C), 1450 (s), 1380 (s), 1290 (s), 1230 (s), 1170 (s), 1110 (s), 1080 (s), 980 (s), 795 (m) cm^{-1}; NMR δ 1.30–1.97 (m, 1 H, $(CH_2)_5$) 2.23 (s, 6 H, CH_3C= and CH_3C=O); mass spectrum, m/e (%) 196 (M^+, 36), 168 (1), 154 (10), 153 (72)er, 140 (9), 43 (100); exact mass calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1098.

3-(Methoxycarbonyl)-4,2′,6′-trimethyl-$\Delta^{3,4}$-2,5-dioxaspiro-[5,4]decane (8c). From diazo ester **3** (1.5 g) and 2,6-dimethylcyclohexanone (6.5 g), compound **8c** (mixture of stereoisomers) was obtained as a yellow liwuid (0.284 g, 18%): bp 100–105 °C (0.5 torr); IR (neat) 1720 (s, C=O), 1670 (s, C=C), 1440 (s), 1350 (s), 1280 (s), 1120 (s), 1050 (s), 985 (s), 680 (s) cm^{-1}; NMR (CCl_4) δ 0.92 (d, 6 H, J = 6.5 Hz, 2 × CH_3CH), 1.30–1.70 (m, 6 H methylenes), 1.90–2.30 (m, 2 H, methynes), 2.25 (s, 3 H, CH_3C=), 3.72 (s, 3 H, COOmE); mass spectrum, m/e (%) 240 (M^+, 13), 183 (29), 109 (13), 69 (57), 59 (22), 55 (36), 43 (80), 41 (100); exact mass calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1360.

3-Acyl-4,2′,6′-trimethyl-$\Delta^{3,4}$-2,5-dioxaspiro[5,4]decane (8d). diazo ketone **5** (2.5 g) and 2,6-dimethylcyclohexanone (8.0 g), yielded dioxol **8d** as a yellow liquid (0.812 g, 18%): bp 78–80 °C (0.05 torr); IR (neat) 1685 (s, C=O), 1640 (s, C=C), 1460 (s), 1390

(s), 1280 (s), 1250 (s), 1180 (s), 1145 (s), 1100 (s), 1060 (m), 940 (s), 790 (m) cm^{-1}; NMR (CCl_4) δ 0.97 (d, 6 H, J = 6.5 Hz, 2 × CH_3CH), 1.23–1.90 (m, 6 H, methylenes), 1.90–2.40 (m, 2 H, methynes), 2.20 (s, 6 H, CH_3C= and CH_3C=O); mass spectrum, m/e (%) 224 (M^+, 32), 168 (912), 167 (89), 154 (16), 43 (100); exact mass calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1406.

3-(Methoxycarbonyl)-3′,4-dimethyl-$\Delta^{3,4}$-$\Delta^{2',3'}$-2,5-dioxaspiro[5,4]decane (9a). Diazo ester **3** (1.0 g) and 3-methylcyclohexenone (4.5 g) yielded compound **9a** as a colorless liquid (0.658, 45%): bp 130–132 °C (2.4 torr); IR (neat) 1730 (s, C=O), 1690 (s, C=C), 1460 (s), 1400 (s), 1240 (s), 1140 (s), 990 (m), 910 (m), 785 (m) cm^{-1}; NMR (CCl_4) δ 1.75 (s, 3 H, methyl on C-3′ (of cyclohexyl ring)), 1.88 (m, 4 H, methylenes), 2.00–2.30 (m, 2 H, allylic methylene), 2.22 (s, 3 H, methyl on dioxole ring), 3.70 (s, 3 H, COOMe), 5.50 (q, 1 H, J = 1.3 Hz, vinyl proton); mass spectrum, m/e (%) 224 (M^+, 64), 206 (13), 196 (54), 125 (82), 121 (20), 111 (26), 109 (18), 93 (33), 91 (26), 82 (34), 79 (100), 77 (33), 43 (59); exact mass calcd for $C_{12}H_{16}O_4$ 224.1048, found 224.1055.

3-Acyl-3′,4-dimethyl-$\Delta^{3,4}$-$\Delta^{2',3'}$-2,5-dioxaspiro[5,4]decane (9b). From diazo ketone **5** (1.5 g) and 3-methylcyclohexenone (5.0 g) compound **9b** was obtained as a colorless liquid (0.951 g, 38%): bp 86–88 °C (0.05 torr); IR (neat) 1690 (s, C=O), 1630 (s, C=C), 1450 (s), 1390 (s), 1280 (s), 1170 (s), 1130 (s), 1090 (s), 1040 (m), 980 (m), 935 (s), 735 (s) cm^{-1}1; NMR (CCl_4)δ 1.73 (s, 3 H, methyl on cyclohexyl ring), 1.75–2.00 (m, 4 H, methylenes), 2.10–2.30 (m, 2 H, allylic methylene), 2.12 (s, 3 H, CH_3C=), 2.20 (s, 3 H, CH_3C=O), 5.55 (q, 1 H, J = 1.5 Hz, vinyl proton); mass spectrum, m/e (%) 208 (M^+, 25), 180 (13), 137 (12), 55 (11), 43 (100); exact mass calcd for $C_{12}H_{16}O_3$ 208.1099, found 108.1092.

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Registry No. **6a**, 81099-78-7; **6b**, 96706-06-8; **6c**, 96706-07-9; **6d**, 96706-08-0; **7a**, 96706-09-1; **7b**, 96706-10-4; **7c**, 96706-11-5; **7d**, 96706-12-6; **7e**, 96706-13-7; **7f**, 96706-14-8; **7g**, 96706-15-9; **7h**, 96706-16-0; **7i**, 96706-17-1; **7j**, 96706-18-2; **7k**, 96706-19-3; **7l**, 96706-20-6; **8a**, 96706-21-7; **8b**, 96706-22-8; **8c**, 96706-23-9; **8d**, 96706-24-0; **9a**, 96706-25-1; **9b**, 96706-26-2; $CH_3COC(=N_2)COOCH_3$, 24762-04-7; $CH_3OCOC(=N_2)COCH_3$, 29397-21-5; $(CH_3)_2CHCHO$, 78-84-2; RCHO (R = 2-furoyl), 98-01-1; CH_3CH=CHCHO, 4170-30-3; CH_3COCH_3, 67-64-1; $CH_3COCH(CH_3)_2$, 563-80-4; $CH_3COCH_2CH(CH_3)_2$, 108-10-1; $CH_3CH_2COCH_2CH_3$, 96-22-0; $CH(CH_3)_2COCH(CH_3)_2$, 565-80-0; $(CH_3)_2CHCH_2COCH_2CH(CH_3)_2$, 108-83-8; cyclohexanone, 108-94-1; 2,6-dimethylcyclohexanone, 2816-57-1; 3-methyl-2-cyclohexen-1-one, 1193-18-6.

An Efficient Diastereoselective Synthesis of 6-Hydroxy-4a-phenyl-*cis*-decahydroisoquinolines through *N*-Acyliminium Ion Induced Polyene Cyclization

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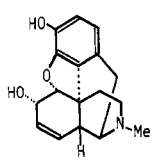
The two kinds of carbamates **13a,b** and **18a,b** were prepared from acids **11** and **17**, respectively, through the Curtius method via the corresponding acid azides. Cyclization of **13a,b** and **18a,b** with paraformaldehyde–formic acid afforded 4a-phenyl-*cis*-decahydroisoquinoline-6-formates **19a,b** with high diastereoselectivity. Reduction of **19a,b** yielded 6-hydroxy-2-methyl-4a-phenyl-*cis*-decahydroisoquinoline (**20a**). The ring juncture of **19** (and **20a**) was determined by conversion of **19b** to *cis*-4a-phenyldecahydroisoquinoline (**25**). The relative configuration of the hydroxyl group at the 6-position of **20a** was determined as cis to the phenyl group by comparison with the alternative isomer **20b** prepared by reduction of **27** derived from **19b**.

In the search for potent and nonaddictive analgesics, morphine (**1**) has been subjected to many modifications.[1] Many synthetic strategies for morphine-based structural variants have been reported in the last decades,[2-7] and various analogues of morphine have been reported. The investigations on structural variants of the morphine molecule have been an area of considerable interest and are still being actively pursued in the hope of finding significant analgesics with fewer undesirable side effects. Of special interest to us is the development of a facile procedure for the synthesis of 6-hydroxy-4a-phenyldecahydroisoquinolines from readily accessible starting materials, since 6-hydroxy-4a-phenyl-*trans*-decahydroisoquinoline (**2a**) can be considered to be a simpler fragment of morphine as drawn in the structures. We wish to report a general and novel synthesis of 6-hydroxy-4a-phenyl-*cis*-decahydroisoquinolines (**2b**), stereoisomers of **2a**, in this paper.



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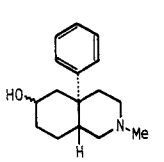
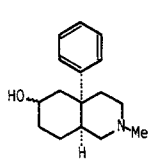


2a



2b

Results and Discussion

The field of biomimetic cationic polyene cyclization reaction has been used for the synthesis of complex multicyclic compounds with excellent sterocontrol.[8,9]

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