Reactions of Dipivaloylketene Dimer with Nucleophiles: New Access to the 2,6,9-Trioxabicyclo[3.3.1]nona-3,7-diene Ring System (Bridged Bis-Dioxines)†

C. Oliver Kappe,‡ Gert Kollenz,*,‡ Walter M. F. Fabian,‡ Curt Wentrup,‖ and Gerald Färber§

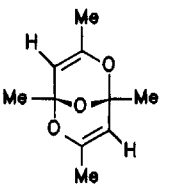
Institute of Organic Chemistry and Institute of Physical Chemistry, Karl-Franzens-University Graz, A-8010 Graz, Austria, and Department of Chemistry, The University of Queensland, Brisbane, Queensland, Australia 4072

Received January 25, 1993

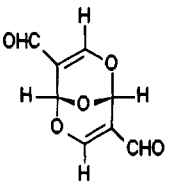
Novel and convenient methods to prepare several functionalized 2,6,9-trioxabicyclo[3.3.1]nonadienes ("bridged bis-dioxines") **6**, **10**, **11**, and **12** are described. In general, these are obtained by addition of nucleophiles to α-oxoketene **5** in a multistep reaction sequence, where the specific reaction pathway depends strongly on the type of nucleophile employed: Aromatic amines with electron-donating substituents afford the trioxabicyclononadienes **6**, while with aliphatic amines or thiolates, 2 equiv of the corresponding dipivaloylacetamides **13** or thioesters **14**, respectively, are formed. In the case of OH nucleophiles, the primary 1:1 adducts **8** are isolable, characterized by an X-ray analysis of **8a**. Under acidic conditions, **8** can be cyclized to the bifunctionalized bis-dioxines **10**. The bis-carboxylic acid **10c** serves as a valuable intermediate to synthesize other derivatives, e.g. the bis-acid chloride **11** and the bis-ester **12**. Mechanistic pathways leading to the various reaction products are discussed in detail and supported by semiempirical molecular orbital calculations using the AM1 method. The spontaneous formation of the bis-dioxine skeleton in the reaction **5** → **6** is likely to proceed via an unusual [4 + 4] type tandem cyclization reaction.

The design and synthesis of polycyclic compounds capable of the selective recognition of metal cations and other species is of great interest to organic chemists. Although many examples of macropolycyclic synthetic ligands capable of complexing metal cations are known, there is an active search for new preorganized receptors (host molecules) with improved complexation properties.[1]

One ligand that exhibits a good ability to coordinate transition metals, but has found little synthetic attention in the past is the rather uncommon 2,6,9-trioxabicyclo-[3.3.1]nona-3,7-diene ring system.[2-4] Currently, there are only two compounds reported, possessing this bicyclic diene structure: the 1,3,5,7-tetramethyl derivative **1**, formed in a multistep Pt^{2+}-promoted condensation reaction from acetylacetone,[2,3] and the 4,8-dicarbaldehyde **2**, identified as a self-condensation product of triformylmethane.[4] These are both dissymmetric molecules having a 2-fold rotational axis as the only element of symmetry and therefore exhibit axial chirality.[2,4a] Separation of **1** into its enantiomers has been achieved via diastereoisomeric rhodium complexes.[2] Heterobicycle **1** is reported to form stable mono- and binuclear complexes with transition metal cations (i.e. Rh^+, Pt^{2+}, or Pd^{2+}), via coordination to its diene system.[2,3]



1



2

In our laboratories we are currently exploring new synthetic pathways leading to this bridged bicyclic ring system and studying its incorporation into larger three-dimensional host molecules. In the present paper,[5] we focus on preparative and mechanistic aspects on the formation of simple mono- and bifunctionalized trioxabicyclononadienes. Our somewhat unconventional approach to this heterocyclic ring system involves the addition of nucleophiles to ketene **5**. This sterically hindered α-oxoketene is extraordinarily stable and can be obtained in high yield by cyclodimerization of dipivaloylketene (**4**).[6]

Results and Discussion

The reaction of oxoketene **5** with aromatic amines was performed in methylene chloride or acetonitrile solution at room temperature. Instead of the expected primary 1:1 adducts of the amines to the ketene functionality in **5**, spontaneous elimination of carbon dioxide occurred, and trioxabicyclononadienes **6a-f** were isolated in good yields (Table I).[7] In addition to spectroscopic data, the

† Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

‡ Institute of Organic Chemistry.

§ Institute of Physical Chemistry.

‖ University of Queensland.

(1) e.g.: (a) An, H.; Bradshaw, J. S.; Krakowiak, K. E.; Zhu, C.; Dalley, N. K.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 4998. (b) An, H.-Y.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1992**, *98*, 543. (c) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245 and refs therein.

(2) De Renzi, A.; Panunzi, A.; Paolillo, L.; Vitagliano, A. *J. Organomet. Chem.* **1977**, *124*, 221.

(3) (a) Gibson, D.; Oldham, C.; Lewis, J.; Lawton, D.; Mason, R.; Robertson, G. B. *Nature (London)* **1965**, *208*, 580. (b) Gibson, D.; Lewis, J.; Oldham, C. *J. Chem. Soc. A* **1967**, 72. (c) Mason, R.; Robertson, G. B. *J. Chem. Soc. A* **1969**, 492.

(4) (a) Arnold, Z.; Budesinsky, M. *J. Org. Chem.* **1988**, *53*, 5352. (b) Podlaha, J.; Podlahova, J.; Arnold, Z.; Maly, K.; Petricek, V. *Acta Crystallogr., Sect C: Cryst. Struct. Commun.* **1988**, *C44*, 1966.

(5) Part of this work was published in preliminary form: Kappe, C. O.; Färber, G.; Wentrup, C.; Kollenz, G. *Tetrahedron Lett.* **1992**, *33*, 4553.

(6) (a) Kappe, C. O.; Evans, R. A.; Kennard, C. H. L.; Wentrup, C. *J. Am. Chem. Soc.* **1991**, *113*, 4234. (b) Kappe, C. O.; Färber, G.; Wentrup, C.; Kollenz, G. *J. Org. Chem.* **1992**, *57*, 7078.

(7) This general reaction **5** → **6** could be successfully extended to aromatic diamines, thus affording "crab-like" molecules having two trioxabicyclononadiene ligands attached to an aromatic ring system.[5]

0022-3263/93/1958-3361$04.00/0

Scheme I

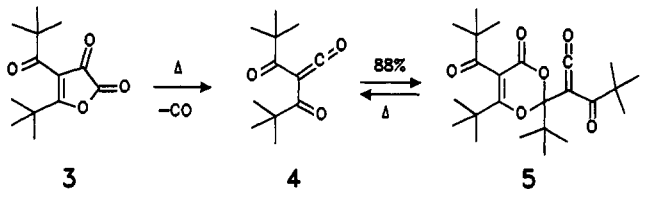
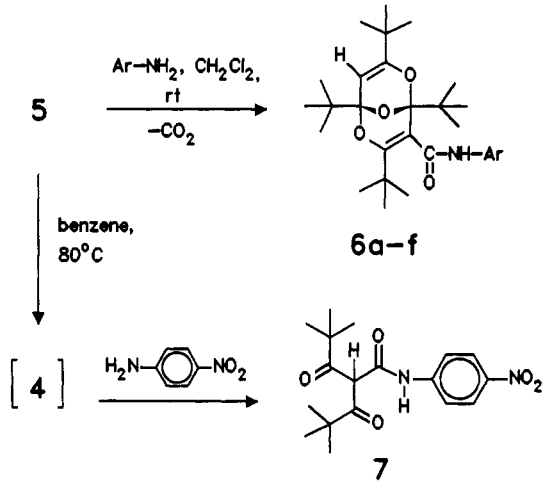


Table I. Reactions of Oxoketene 5 with Aromatic Amines (5 → 6)

product	Ar	reaction time (h)	isolated yield (%)
6a	phenyl	24	74
6b	4-(MeO)-phenyl	6	95
6c	4-(Me_2N)-phenyl	2	83
6d	4-(H_2N)-phenyl	1	78
6e	2-(H_2N)-phenyl	24	62
6f	2-naphthyl	48	86

Scheme II



structure of **6a** was confirmed by X-ray crystallographic analysis.[5] The progress of the reaction, which was followed by thin-layer chromatography, revealed a pronounced substituent effect on the overall reaction time (Table I). Electron-donating substituents on the aromatic ring accelerate the reaction, whereas electron-withdrawing substituents, as in *p*-nitroaniline, completely prevent the reaction. Steric hindrance also increases the reaction time (**6e,f**). It should be noted that in the transformation of **5** → **6** no intermediates or side products are isolable. Although *p*-nitroaniline does not react with dipivaloylketene dimer **5** at room temperature, the reaction of 2 equiv of amine with **5** in refluxing benzene yielded dipivaloylacetanilide **7**. The formation of **7** can be explained in terms of thermal monomerization of dimer **5** under the reaction conditions employed.[6b]

When alcohols were employed as nucleophiles, a different reaction pathway was observed: In contrast to the reaction with aromatic amines (**5** → **6**), here, the primary addition products **8a,b** were isolated upon treatment of **5** with excess ethanol or methanol at room temperature. Similar results were obtained when **5** was reacted with aqueous acetonitrile, leading to carboxylic acid **8c**. These β-keto carboxylic acid derivatives **8** exist exclusively in the enol form in solution, as seen by ^1H and ^{13}C NMR spectroscopy, and, due to steric hindrance by the two bulky substituents, adopt the energetically preferred *E*-configuration.[8] For ester **8a** this was confirmed by X-ray crystallographic analysis (Figure 1).[9] Carboxylic acid **8c**

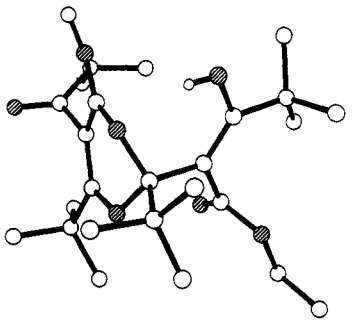
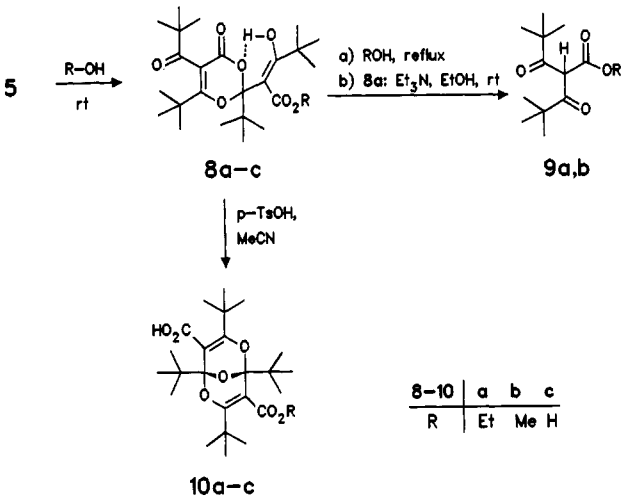


Figure 1. Molecular structure of **8a**. Circles shaded from top right to bottom left represent oxygen atoms. The length of the intramolecular hydrogen bond is 2.656(4) Å.

Scheme III



is one of the few stable open-chained β-keto carboxylic acids known.[8a] Its kinetic stability toward decarboxylation can be explained by the rather high activation barrier necessary for conversion of the *E*-enol into the keto form, which is required for a concerted decarboxylation process.[8a] Prolonged action of water on **8c** resulted in degradation of the dioxinone ring and ultimately gave dipivaloylmethane. Much in the same way, treatment of **8a,b** with refluxing ethanol or methanol, respectively, provided 2 equiv of the corresponding dipivaloylacetic esters **9a,b**. The methyl ester **9b** has also been obtained previously by direct addition of methanol to monomeric dipivaloylketene (**4**).[6a]

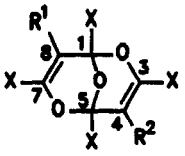
Conversion to the trioxabicyclononadiene ring system from the primary addition products **8a–c** was achieved in an acid-catalyzed cyclization reaction.[10] Hence, treatment of **8a–c** with *p*-toluenesulfonic acid in acetonitrile, or with

(8) Open-chain β-keto carboxylic esters and acids with bulky *aromatic* substituents (e.g. mesityl) are known to exist predominantly in the *E*-configured enol form and have been isolated in pure state: (a) Meier, H.; Wengenroth, H.; Lauer, W.; Krause, V. *Tetrahedron Lett.* **1989**, *30*, 5253. (b) Meier, H.; Wengenroth, H.; Lauer, W.; Vogt, W. *Chem. Ber.* **1988**, *121*, 1643. (c) Meier, H., Lauer, W.; Krause, V. *Chem. Ber.* **1986**, *119*, 3382. (d) Meier, H.; Lauer, W.; Scholter, F. U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 350.

(9) To the best of our knowledge this is the first X-ray structure of a conventional open-chain β-keto carboxylic ester that shows *E*-configuration; however, see: Antipin, M. Yu.; Kalinin, A. E.; Struchkov, Yu. T.; Aladzheva, I. M.; Mastryukova, T. A.; Kabachnik, M. I. *Zh. Strukt. Khim.* **1978**, *19*, 319. The author has deposited atomic coordinates for this structure (**8a**) with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(10) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098.

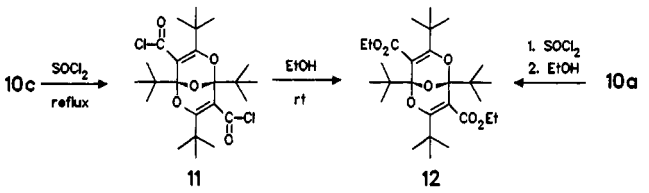
Table II. ^{13}C NMR Data in $CDCl_3$ for Trioxabicyclononadienes



no.	R^1	R^2	C-1/C-5	C-3/C-7	C-4/C-8	CO–R
6a	H	CONHPh	97.1 m/ 99.6 m	161.7 m/ 162.1 m	105.5 s/ 92.0 d[a]	167.0 s
10a	CO_2H	CO_2Et	98.2 m/ 98.4 m	163.0 m/ 163.5 m	102.1 s/ 102.7 s	169.3 t[b]/ 175.6 s
10c[c]	CO_2H	CO_2H	99.0 m	162.7 m	104.1 s	171.0 s
11	COCl	COCl	98.2 m	163.4 m	109.3 s	170.5 s
12	CO_2Et	CO_2Et	98.1 m	162.5 m	102.8 s	169.3 t[b]

[a] $^1J_{CH}$ = 164 Hz. [b] $^3J_{CH}$ = 2.5 Hz. [c] Recorded in acetone-d_6.

Scheme IV



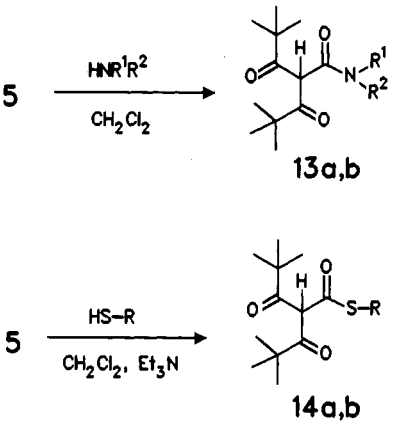
boron trifluoride etherate in dry ether, afforded the carboxylic acids **10a–c**. If water was to be used as nucleophile, it was most convenient to run the addition reaction directly in the presence of *p*-TsOH and not to isolate the intermediate **8c**. In that way the bis-carboxylic acid **10c** could be isolated in up to 81% yield in a one-pot reaction from **5**. The close structural relationship of the bicycles **6** and **10** was made evident by ^{13}C NMR data (Table II).

However, it should be pointed out that the mechanism leading to either mono- (**6**) or bifunctionalized bis-dioxines (**10**) are distinctly different from each other (see below). Note that in the reaction of ketene **5** with aromatic amines, the decarboxylated products **6a–f** are formed, whereas in the reaction with alcohols or water the resulting bicycles **10a–c** still contain the carboxylic acid functionality. Under no conditions (base or acid catalysis, heat) were we able to decarboxylate the acids **10** to monofunctionalized derivatives related to **6**.

The bis-acid **10c** is a valuable starting material for the synthesis of several further functionalized derivatives (Scheme IV): Treatment with thionyl chloride provided the bis-acid chloride **11**, which was reacted with ethanol to form the bis-ester **12**. The same compound is obtained too upon subsequent reaction of **10a** with thionyl chloride and ethanol, which further corroborates the structures for bicycles **10–12**.

Upon treatment with strong nucleophiles, such as aliphatic amines or thiolates, ketene **5** showed yet another type of reaction: When a methylene chloride solution of the oxoketene was treated with 2 equiv of benzylamine or diethylamine at room temperature the only isolable products (2 equiv) were the corresponding N-substituted dipivaloylacetamides **13a,b**. Even the slow addition of only 1 equiv of benzylamine at −50 °C to a solution of **5** did not enable us to isolate the primary 1:1 adduct, but again afforded **13a** apart from unchanged **5**. Similar results were obtained with thiolates leading to thioesters **14a,b**. Although the thiols themselves did not react with ketene **5**, catalytic amounts of triethylamine initiated the rapid conversion into the final products **14a,b**. In all these cases

Scheme V



degradation of the dioxinone ring occurred, and products, formally derived from monomeric dipivaloylketene (**4**) were formed within seconds in almost quantitative yield. Note that these reactions proceed at room temperature and are not related to the thermally induced reaction sequence **5** → **4** → **7** (Scheme II).

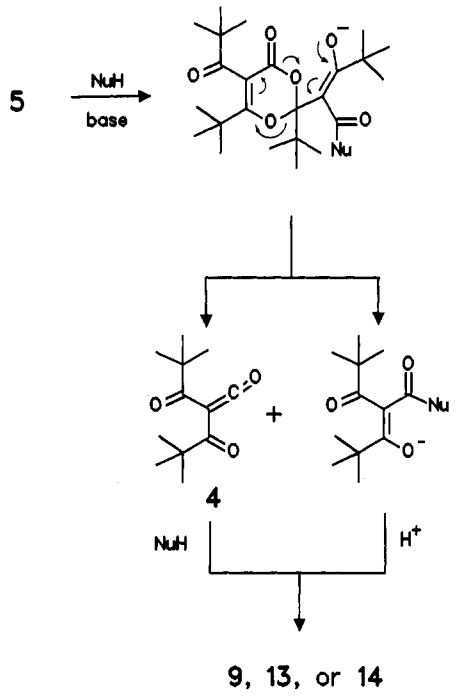
In addition, the results of several further experiments should be emphasized in this context period. Reaction of aniline with ketene **5** *in the presence of triethylamine* did not give bis-dioxine **6a**, as obtained in the uncatalyzed experiment, but furnished dipivaloylacetanilide (**13c**) in high yield. In contrast, acid catalysis did not change the outcome of the transformation **5** → **6a**. In a control experiment we showed that the ketene **5** itself remains unaffected by triethylamine; no base-catalyzed monomerization **5** → **4** occurred, which could also eventually lead to products of type **13**. This prompted us to study the effect of base catalysis also on the potential fragmentation of the ketene–ethanol adduct **8a**. Indeed, when a suspension of **8a** in ethanol was treated with a catalytic amount of triethylamine, an analogous fragmentation took place, and 2 equiv of **9a** could be isolated in quantitative yield.

Mechanistic Aspects. From all these experiments the following conclusions can be drawn: (a) The primary reaction step in all reactions of nucleophiles with α-oxoketene **5** described herein should be the addition of the nucleophile to the ketene functionality,[11] although (b) the resulting primary adducts are only isolable when alcohols or water are employed as nucleophiles (Scheme III). In the presence of strong bases, or in cases where the nucleophile is a strong base itself (i.e. diethylamine) *subsequent* fragmentation of the dioxinone ring occurs, and 2 equiv of the corresponding dipivaloylacetic acid derivatives (**9**, **13**, or **14**) are formed via two consecutive elimination processes[12] (Scheme VI). It should be noted again that the ketene **5** itself is not affected by the strong base triethylamine; thus, a simple nucleophilic attack on the lactone moiety of the dioxinone ring seems unlikely.[13]

(11) The exact nature of the primary addition of nucleophiles to ketenes, while irrelevant to the present study, has been the subject of some recent debate: (a) Allen, A. D.; McAllister, M. A.; Tidwell, T. T. *Tetrahedron Lett.* **1993**, *34*, 1095. (b) Allen, B. A.; Hegarty, A. F.; O'Neill, P.; Nguyen, M. T. *J. Chem. Soc., Perkin Trans. 2* **1992**, *927*. (c) Andraos, J.; Kresge, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 5643. (d) Allen, A. D.; Andraos, J.; Kresge, A. J.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1992**, *114*, 1878. (e) Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273, and refs therein. (f) Leung-Toung, R.; Wentrup, C. *Tetrahedron* **1992**, *48*, 7641. *J. Org. Chem.* **1992**, *57*, 4850. (g) Freiermuth, B.; Wentrup, C. *J. Org. Chem.* **1991**, *56*, 2286.

(12) (a) Royals, E. E.; Brannock, K. C. *J. Am. Chem. Soc.* **1954**, *76*, 3041. (b) Srikrishana, A.; Krishnan, K. *Tetrahedron Lett.* **1988**, *29*, 4995.

Scheme VI

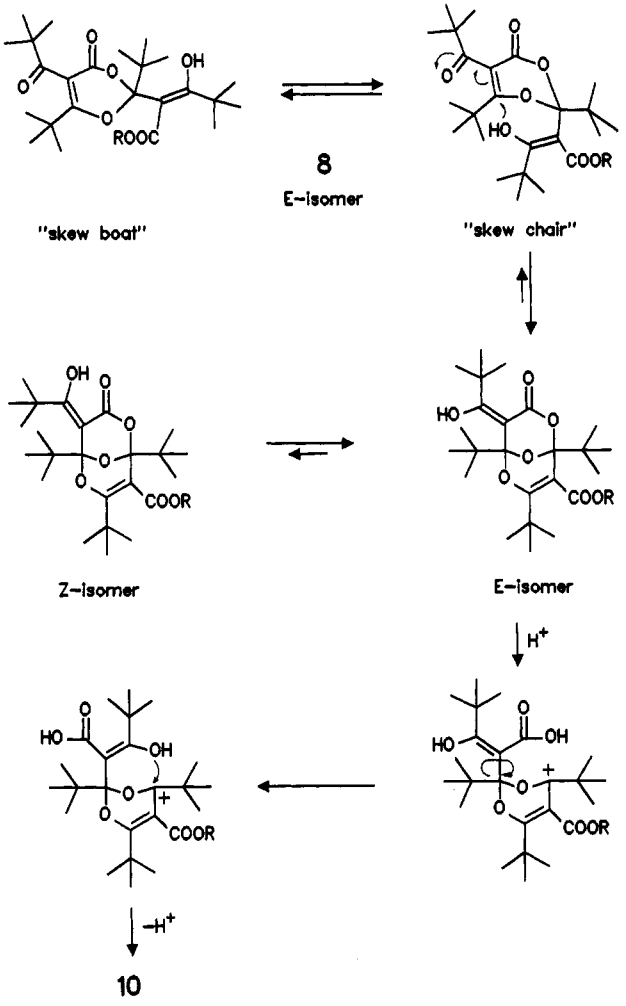


A reasonable mechanistic pathway leading to the bicyclononadienes **10** (**8** → **10**, cf. Scheme III) is outlined in Scheme VII in which the bis-dioxine skeleton is formed by intramolecular Michael addition[10] of the enolic OH group to the cross-conjugated α,β-unsaturated carbonyl system in *E*-**8**. From molecular models it can easily be seen that a *Z*-configured starting material **8** would *not* be able to undergo this cyclization reaction. During the formation of the bicyclic intermediate, another problem of *E*/*Z*-isomerism arises again: The *E*-configuration should predominate due to steric interaction of the bulky *tert*-butyl groups within the *Z*-isomer. Acid-promoted ring opening[14] affords a well-stabilized carbocation[15] which then recyclizes to the final product **10**. This step again requires *E*-configuration of the enolic acid side chain, so that the OH group is in the correct position for the final ring closure.

From our experimental findings (see above), it becomes clear that the reaction pathway **5** → **6** must be distinctly different from the sequence **5** → **8** → **10**. Most importantly, it has to be considered that bicycles of type **10** could *not* be decarboxylated to give monofunctionalized derivatives of type **6**. It is therefore highly unlikely that any bifunctionalized bicyclic derivative related to **10** is an intermediate in the sequence **5** → **6**, thus eliminating the possibility of decarboxylation as the final step of the reaction sequence. An alternative is suggested in Scheme VIII. After decarboxylation from the keto form[8a] and tautomerization, an oxygen-bridged double 1,3-oxadiene intermediate is formed, which, surprisingly—depending on its specific conformation—can cyclize to the final bis-dioxine system **6** via a [4 + 2] hetero-Diels–Alder reaction or a [4 + 4]-type "tandem" cyclization.

To get some more insight into the mechanism of this particular reaction step, semiempirical molecular orbital

Scheme VII



calculations by the AM1 method[18,19] on the model compound **A** were performed (Scheme IX). In both the [4 + 2] and the [4 + 4] pathways a bond between C1 and O9 in **A** will be formed, whereas the second bond will join either O4–C8 [4 + 2] or O4–C6 [4 + 4]. Thus, for the [4 + 4] pathway, the distance *r* (O4–C6) was chosen as a reaction coordinate. The structure for the transition state **TS** obtained in this way is shown in Figure 2 and relevant energy and structure data are given in Table III. Downhill optimizations along both directions of the normal mode corresponding to the imaginary frequency either led back

(13) Iwaoka, T.; Murdiaschi, T.; Sato, M.; Kaneko, C. *Synthesis* **1992**, *977*, and refs therein.

(14) Acid catalysis may also accelerate the Michael addition itself by protonation (or complexation) of one or both carbonyl oxygens.

(15) March, J. *Advanced Organic Chemistry*; Wiley: New York, 1992; pp 165–174.

(16) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325.

(17) This reaction can also be classified as a further example of a "tandem" cyclization process[20] and, interestingly, corresponds perfectly with the key step of the mechanism proposed for the formation of dicarbaldehyde **2** (via self-condensation of triformylmethane), although the authors[4a] did not specifically emphasize this unusual [4 + 4] reaction pathway.

(18) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(19) All calculations were done with VAMP 4.4 (vectorized AMPAC) using the keyword PRECISE throughout. A Stardent version was kindly provided by Dr. T. Clark, Institut für Organische Chemie der Universität Erlangen—Nürnberg, Germany. Transition states were refined by gradient norm minimization (routine NS01A in VAMP) and fully characterized by force constant calculations as well as downhill optimizations. Starting structures were generated by the SYBYL 5.5 (Tripos Associates, Inc., St. Louis, MO) molecular modeling package.

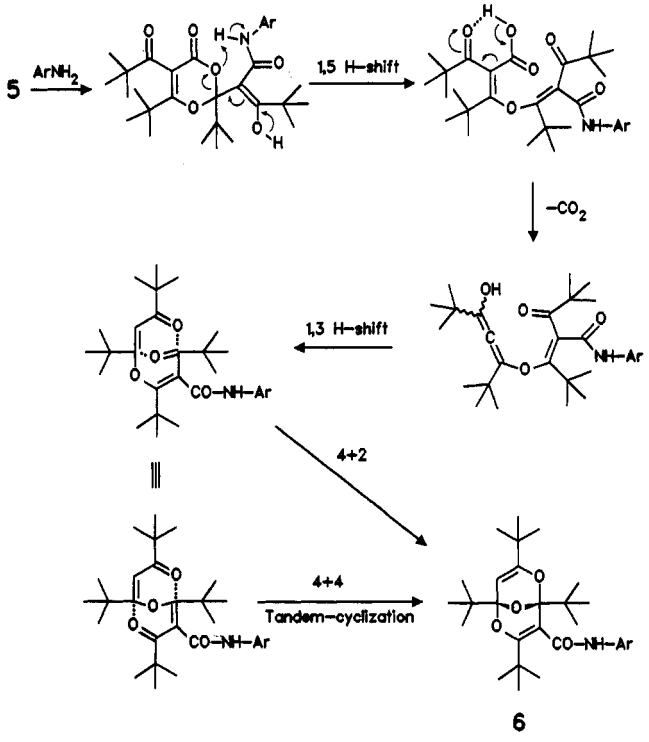
(20) (a) Kaupp, G.; Pogodda, U.; Affah, A.; Meier, H.; Vierengel, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 768. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1332. (c) Rubin, M. B.; Bergurie, M.; Kosti, S.; Kaftory, M. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2670. (d) Rubin, M. B.; Sander, W. W. *Tetrahedron Lett.* **1987**, 5137. (e) Ho, Tse-Lok *Tandem Organic Reactions*; J. Wiley & Sons: New York, 1992.

Table III. Calculated Heats of Formation (ΔH_f, kcal mol^{-1}), Dipole Moments μ (Debye), Ionization Potentials (eV), Imaginary Frequencies $\tilde{\nu}$ (cm^{-1}) for Transition States, and Selected Structural Parameters (distances in pm, torsional angles in degrees) of the Model Compounds

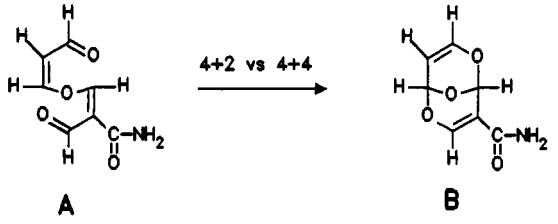
	ΔH_f	μ	IP	$\tilde{\nu}$	C1–O5	C1–O9	O4–C6	O5–C6	O4–C8	C8–C9	C3–O4	τ_1[a]	τ_2[b]	τ_3[c]	τ_4[d]
A	−99.9	4.16	10.34	–	138.1	262.2	254.7	138.4	377.0	123.5	123.9	105.9	174.3	−87.8	174.4
TS	−80.0	7.33	8.97	559	136.3	228.9	167.3	141.5	345.4	125.2	128.7	100.5	167.8	−88.5	−178.5
B	−122.7	3.63	10.11	–	142.2	143.9	143.4	142.3	334.4	136.5	137.9	104.1	168.7	−78.9	170.7
C	−99.9	4.16	10.34	–	262.6	138.0	409.0	123.5	254.6	138.4	123.9	−92.3	−174.7	−105.9	−173.9
TS′	−77.8	1.60	8.78	605	166.7	142.1	351.4	128.5	220.9	136.0	126.3	−95.9	−168.2	−96.0	178.2
D	−122.7	3.63	10.11	–	143.9	142.2	334.4	136.5	143.4	142.3	137.8	−102.7	−170.7	−104.1	−168.7

[a] τ_1: O4–C6–C7–C8 in **A**, **TS**, **B**; O5–C1–C2–C3 in **C**, **TS′**, **D**. [b] τ_2: C6–O4–C13–H15 in **A**, **TS**, **B**; C1–O5–C6–H16 in **C**, **TS′**, **D**. [c] τ_3: O9–C1–C2–H14 in **A**, **TS**, **B**; O4–C8–C7–C6 in **C**, **TS′**, **D**. [d] τ_4: C1–O9–C8–H17 in **A**, **TS**, **B**; C8–O4–C3–H15 in **C**, **TS′**, **D**.

Scheme VIII



Scheme IX



to the starting structure **A** or the expected cycloadduct **B**, thus corroborating **TS** as the correct transition structure for the formal [4 + 4] cycloaddition. A similar calculation using *r* (O4–C8) as a reaction coordinate failed. To avoid a conformational bias of **A** toward a [4 + 4] pathway (*r* (O4–C6) = 255 pm versus *r* (O4–C8) = 377 pm), a [4 + 2] cycloreversion process starting from the product **B** with *r* (O4–C6) and *r* (C1–O5) as reaction coordinates was calculated. The transition structure **TS′** obtained in this way is shown in Figure 2. Downhill optimizations did not lead back to **B** but resulted in either the expected ring-opened structure **C** or structure **D**, i.e. to a structure resulting from a [4 + 4] rather than a [4 + 2] cycloaddition. Thus, both **TS** and **TS′** correspond to transition states for the [4 + 4] pathway. Both structures merely differ in the advancement of the two forming bonds: in **TS** the formation of the C1–O9 bond lags behind O4–C6, whereas in **TS′** the bond to C1 is more advanced. All other attempts to locate a [4 + 2] transition state also failed. Hence, these model calculations strongly support a [4 + 4] pathway for this reaction. It should be noted that despite the formally symmetry-forbidden character (see below) of such a reaction type, no intermediate was obtained. Therefore, we conclude that this reaction is a concerted albeit asynchronous process. A rationalization for this easy [4 + 4] pathway can be deduced from considering the transition state structure. To define the mode of attack, the four dihedral angles τ_1–τ_4 are used (τ_1 and τ_3 describe the plane of the C=C and τ_2 and τ_4 that of the C=O double bonds, respectively). The values of these dihedral angles given in Table III clearly indicate *an attack in the plane of the carbonyl groups*. This means that the π-orbitals of the heterodiene fragments interact with the oxygen lone pairs rather than with the π-orbitals of the carbonyl groups. Hence, this is not a pericyclic but a pseudopericyclic reaction,[16] and it cannot be orbital symmetry forbidden.[17]

Conclusion

In the present paper we have disclosed novel and convenient methods for the preparation of several derivatives of the 2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene ring system. Contrary to the previous methods available,[2-4] which were of restricted synthetic value, our access to this rather uncommon heterocyclic system allows for the synthesis of a number of different mono- and bifunctionalized derivatives. For example, the readily available biscarboxylic acid **10c** can be expected to serve as a valuable intermediate for the preparation of a large variety of other substituted derivatives (cf. Scheme IV), including polycyclic compounds. Furthermore, in view of the known good coordinating ability of these bicyclic diene systems,[2,3] interesting complexation properties of the highly lipophilic novel trioxabicyclononadienes (e.g. **6**, **10**, and **12**) are anticipated and currently under investigation.

Experimental Section

Melting points are uncorrected. Analytical instruments were as previously described.[6b] ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz.

α-Oxoketene **5** was prepared according to our improved procedure.[6b] All other reagents were purchased from Aldrich Chemical Co. and used without further purification. Acetonitrile was dried over 3-Å molecular sieves.

***N*-Aryl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4-carboxamides (6a–f). General Procedure.** To a solution of ketene **5** (210 mg, 0.5 mmol) in dry CH_2Cl_2 was added 2 mL (0.52 mmol) of the corresponding aromatic amine (cf. Table I). After the solution was kept at rt for the period indicated in Table I (1–48 h, TLC-control), the solvent was removed on a rotary evaporator and the resulting residue digested with cold acetonitrile to give

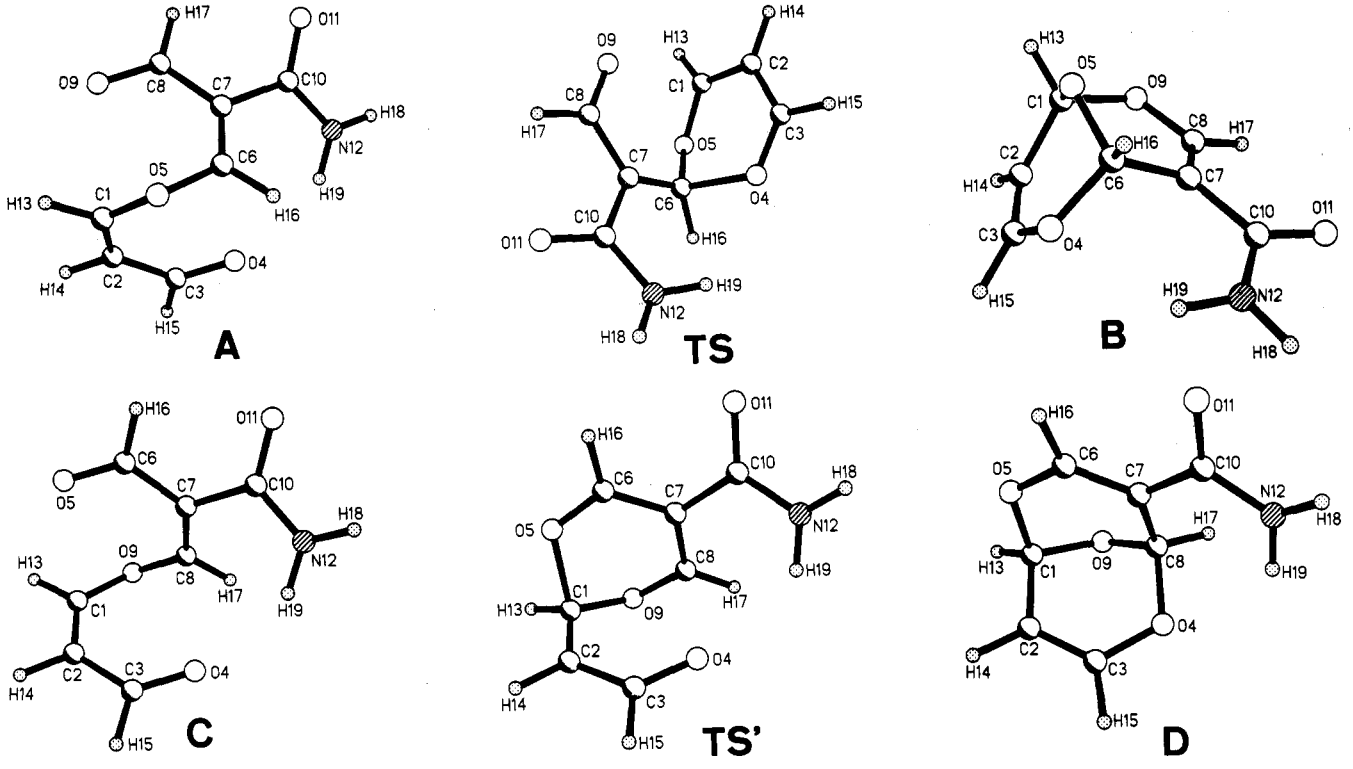


Figure 2. Calculated structures of the model compounds **A–D** and transition states **TS** and **TS'** (AM1).

6a–f (Table I). Analytical samples were prepared by recrystallization from acetonitrile.

6a: mp 120–122 °C; IR (KBr) 3430, 3000–2860, 1665, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.13, 1.22, 1.25 (4 s, 9 H each, 4 *t*-Bu), 4.87 (s, 1 H, H-8), 7.05–7.53 (m, 5 H, Ar-H); ^{13}C NMR see Table II. Anal. Calcd for $C_{29}H_{43}NO_4$: C, 74.16; H, 9.23; H, 2.98. Found: C, 74.16; H, 8.70; N, 2.83.

6b: mp 166–167 °C; IR (KBr) 3420, 3000–2860, 1660, 1610, 1590 cm^{-1}; ^1H NMR (a) in $CDCl_3$ δ 1.02, 1.12, 1.18, 1.21 (4 s, 9 H each, 4 *t*-Bu), 3.78 (s, 3 H, OMe), 4.87 (s, 1 H, H-8), 6.83, 7.39 (2 d, J = 8 Hz, 4 H, Ar-H), 7.12 (br, 1 H, NH); (b) with Eu[hfc]$_3$ δ = 1.22 and 1.24, 1.54 and 1.56 and 1.61 and 1.69, 1.74 and 1.80 (8 s, 36 H, 4 *t*-Bu), 3.48 and 3.52 (2 s, 3 H, OMe), 5.23 and 5.28 (2 s, 1 H, H-8), 6.40 and 8.10 (2 m, 4 H, Ar-H). Anal. Calcd for $C_{30}H_{45}NO_5$: C, 72.11; H, 9.08; N, 2.80. Found: C, 71.93; H, 8.95; N, 2.88.

6c: mp 166–168 °C; IR (KBr) 3430, 3000–2870, 1660, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.02, 1.11 (2 s, 9 H each, 2 *t*-Bu), 1.18 (s, 18 H, 2 *t*-Bu), 2.85 (s, 6 H, NMe_2), 4.84 (s, 1 H, H-8), 6.70, 7.37 (2 d, J = 10 Hz, 4 H, Ar-H). Anal. Calcd for $C_{31}H_{48}N_2O_4$: C, 72.62; H, 9.44; N, 5.46. Found: C, 72.74; H, 9.57; N, 5.56.

6d: mp 190–192 °C; IR (KBr) 3440, 3370, 3000–2870, 1660, 1630, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03, 1.12, (2 s, 9 H each, 2 *t*-Bu), 1.23 (s, 18 H, 2 *t*-Bu), 3.30 (br, 2 H, NH_2), 4.84 (s, 1 H, H-8), 6.62, 7.25 (2 d, J = 9 Hz, 4 H, Ar-H), 7.04 (br, 1 H, NH). Anal. Calcd for $C_{29}H_{44}N_2O_4$: C, 71.87; H, 9.15; N, 5.78. Found: C, 71.90; H, 8.96; N, 5.75.

6e: mp 70–72 °C; IR (KBr) 3420, 3360, 3000–2870, 1660, 1625, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.18, 1.20, 1.27 (4 s, 9 H each, 4 *t*-Bu), 4.01 (br, 2 H, NH_2), 4.87 (s, 1 H, H-8), 6.70–7.18 (m, 5 H, Ar-H and NH). Anal. Calcd for $C_{29}H_{44}N_2O_4$: C, 71.87; H, 9.15; N, 5.78. Found: C, 71.71; H, 9.24; N, 5.81.

6f: mp 200–202 °C; IR (KBr) 3430, 3000–2870, 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08, 1.18, 1.25, 1.29 (4 s, 9 H each, 4 *t*-Bu), 4.90 (s, 1 H, H-8), 7.31–7.51 and 7.72–7.85 (2 m, 7 H, Ar-H and NH), 8.28 (s, 1 H, Ar-H). Anal. Calcd for $C_{33}H_{45}NO_4$: C, 76.26; H, 8.73; N, 2.70. Found: C, 75.88; H, 8.73; N, 2.67.

***N*-(*p*-Nitrophenyl)dipivaloylacetamide (7).** A solution of ketene **5** (210 mg, 0.5 mmol) and *p*-nitroaniline (140 mg, 1 mmol) in dry benzene (3 mL) was heated under reflux for 3 h. After the solvent was evaporated, the residue was digested with hexane and then recrystallized from cyclohexane to give 295 mg (85%) of **7**, mp 130 °C; IR (KBr) 3360, 3000–2870, 1725, 1690, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12, (s, 18 H, 2 *t*-Bu), 5.82 (s, 1 H, H-2), 7.78, 8.27 (2 d, J = 10 Hz, 4 H, Ar-H), 10.08 (br, 1 H, NH). Anal. Calcd for $C_{18}H_{24}H_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found : C , 62.13; H, 6.93; N, 7.99.

(*E*)-2-[1-(Ethoxycarbonyl)-3-hydroxy-3,3-dimethyl-1-butenyl]-2,6-di-*tert*-butyl-5-pivaloyl-1,3-dioxin-4(2*H*)-one (8a). A suspension of ketene **5** (420 mg, 1 mmol) in anhyd ethanol (6 mL) was stirred at rt. After ca. 15 min the ketene had completely dissolved, and shortly thereafter **8a** began precipitating from the solution. The reaction mixture was kept at 4 °C for an additional 2 h and finally was filtered to give 410 mg of **8a**, mp 96–99 °C; IR (KBr) 3500, 3000–2870, 1725, 1690, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 18 H, 2 *t*-Bu), 1.18, 1.28 (2 s, 9 H each, 2 *t*-Bu), 1.30 (m, 3 H, CH_2CH_3), 4.10 (q, J = 7 Hz, 2 H, OCH_2), 7.41 (br, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 100.9 (s, C-5), 107.2 (s, C-1'), 109.2 (m, C-2), 159.4 (s, C-4), 167.3 (t, J = 2.5 Hz, ester CO), 167.7 and 175.8 (2 m, C-6 and C-2'), 210.4 (m, pivaloyl CO). Anal. Calcd for $C_{26}H_{40}O_7$: C, 66.93; H, 9.07. Found: C, 66.95; H, 8.98.

(*E*)-2-[3-Hydroxy-1-(methoxycarbonyl)-3,3-dimethyl-1-butenyl]-2,6-di-*tert*-butyl-5-pivaloyl-1,3-dioxin-4(2*H*)-one (8b). This compound was obtained analogously to **8a** by employing methanol (3 mL) as nucleophile (80%): mp 87–89 °C; IR (KBr) 3495, 3000–2870, 1720, 1695, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 18 H, 2 *t*-Bu), 1.21, 1.31 (2 s, 9 H each, 2 *t*-Bu), 3.67 (s, 3 H, OMe), 7.44, br, 1 H, OH). Anal. Calcd for $C_{25}H_{40}O_7$: C, 66.35; H, 8.91. Found: C, 66.11; H, 8.99.

(*E*)-2-[1-Carboxy-3-hydroxy-3,3-dimethyl-1-butenyl]-2,6-di-*tert*-butyl-5-pivaloyl-1,3-dioxin-4(2*H*)-one (8c). To a solution of ketene **5** (210 mg, 0.5 mmol) in acetonitrile (2.5 mL) water (40 mg, 2 mmol) was added. After 3 d at rt, the solvent was removed on a rotary evaporator. Any dipivaloylketene, formed as a byproduct, was removed from the crystalline product in vacuum (10^{-3} mbar). The crude product was digested with hexane to yield 80 mg (40%) of **8c**, mp 123 °C dec; IR (KBr) 3500, 3300–3000, 3000–2870, 1725, 1690, 1675, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18, 1.20, 1.26, 1.30 (4 s, 9 H each, 4 *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 100.0, 107.1, 109.5, 159.2, 168.8, 173.3, 175.8, 210.2. Anal. Calcd for $C_{24}H_{38}O_7$: C, 65.73; H, 8.73. Found: C, 65.67; H, 8.72.

Ethyl Dipivaloylacetate (9a). (a) By Thermal Fragmentation of 8a. A solution of **8a** (470 mg, 1 mmol) in ethanol (10 mL) was refluxed for 4 h. Evaporation of the solvent gave 510 mg (100%) of ester **9a**.

(b) By Catalytic Fragmentation of 8a. To a suspension of **8a** (235 mg, 0.5 mmol) in dry ethanol (2 mL) was added triethylamine (20 mg) with stirring. After 30 min, the resulting solution was evaporated to leave 255 mg (100%) of **9a**. An analytical sample was obtained by sublimation (50 °C, 10^{-1} mbar): mp 59–61 °C; IR (KBr) 3000–2860, 1735, 1710, 1700sh cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 18 H, 2 *t*-Bu), 1.24 (t, J = 7 Hz, 3 H, CH_2CH_3), 4.22 (q, J = 7 Hz, 2 H, OCH_2), 5.38 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 14.0, 26.7, 45.4, 62.0, 62.2, 165.4, 205.1. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.85; H, 9.42.

Methyl Dipivaloylacetate (9b). This compound was obtained analogously to **9a** (method a) using methanol as reagent (100%): mp 49–50 °C; IR and NMR data are identical with those previously reported.[6a]

1,3,5,7-Tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarboxylic Acid Monoethyl Ester (10a). To a solution of ester **8a** (470 mg, 1 mmol) in dry acetonitrile (3 mL) was added a catalytic amount of p-TsOH and the reaction mixture heated to 60 °C under stirring for 30 min. After evaporation of the solvent, the crude reaction product was recrystallized from acetonitrile to give 350 mg (75%) of **10a**: mp 180–182 °C; IR (KBr) 3250–3000, 3000–2870, 1720, 1685, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.09, 1.18, 1.24 (4 s, 9 H each, 4 *t*-Bu), 1.18–1.34 (m, 3 H, CH_2CH_3), 3.98–4.28 (m, 2 H, OCH_2); ^{13}C NMR see Table II. Anal. Calcd for $C_{26}H_{42}O_7$: C, 66.93; H, 9.07. Found: C, 67.20; H, 8.88.

1,3,5,7-Tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarboxylic Acid Monomethyl Ester (10b). This compound was prepared analogously to **10a** starting form ester **8b** (72%): mp 155–158 °C; IR (KBr) 3300–3000, 3000–2870, 1725, 1690, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.07, 1.19, 1.23 (4 s, 9 H each, 4 *t*-Bu), 3.64 (s, 3 H, OMe). Anal. Calcd for $C_{25}H_{40}O_7$: C, 66.35; H, 8.91. Found: C, 66.44; H, 8.82.

1,3,5,7-Tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarboxylic Acid (10c). (a) From Acid 8c. A solution of acid **8c** (220 mg, 0.5 mmol) in dry acetonitrile (2 mL) containing catalytic amounts of *p*-TsOH was kept for 48 h at rt. Evaporation of the solvent left 180 mg (80%) of **10c**.

(b) From Ketene 5 and H_2O. To a solution of ketene **5** (420 mg, 1 mmol) in acetonitrile (5 mL) containing catalytic amounts of *p*-TsOH was added H_2O (300 mg). After 48 h at rt and an additional 12 h at 4 °C, the precipitated crystals were filtered to give 350 mg (81%) of **10c**. An analytical sample may be obtained by crystallization from acetonitrile: mp 206–207 °C dec; IR (KBr) 3400–3000, 3000–2870, 1690, 1620 cm^{-1}; ^1H NMR (DMSO) δ 1.06, 1.21 (2 s, 18 H each, 4 *t*-Bu); ^{13}C NMR see Table II. Anal. Calcd for $C_{24}H_{38}O_7$: C, 65.73; H, 8.73. Found: C, 65.85; H, 8.91.

1,3,5,7-Tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarbonyl Chloride (11). A mixture of bis-acid **10c** (440 mg, 1 mmol) and freshly distilled thionyl chloride (4 mL) was refluxed under stirring for 1 h. After most of the solvent was removed on a rotary evaporator, any additional unreacted thionyl chloride and HCl was removed in vacuum (10^{-3} mbar). The acid chloride **11** obtained in this procedure (450 mg, 95%) was essentially pure (IR, mp). An analytical sample was obtained by recrystallization from dry acetonitrile: mp 204–206 °C; IR (KBr) 3000–2870, 1770, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12, 1.33 (2 s, 18 H each, 4 *t*-Bu); ^{13}C NMR see Table II. Anal. Calcd for $C_{24}H_{36}Cl_2O_5$: C, 60.63; H, 7.63. Found: 60.35; H, 7.49.

1,3,5,7-Tetra-*tert*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarboxylic Acid Diethyl Ester (12). (a) From Acid Chloride 11. To a solution of the crude acid chloride **11** (475 mg, 1 mmol) in dry CH_2Cl_2 (2 mL) was added ethanol (0.5 mL). After the reaction mixture was kept at rt for 6 h, the solvent was removed in vacuum and the resulting solid recrystallized from acetonitrile to give 390 mg (79%) of **12**.

(b) From Acid 10a. A mixture of acid **10a** (470 mg, 1 mmol) and freshly distilled thionyl chloride (4 mL) was refluxed under stirring for 1 h. After most of the solvent was removed on a rotary evaporator, dry ethanol (2 mL) was added to the oily reaction mixture and after 2 h the precipitated crystals (4 °C) were filtered to yield 350 mg (71%) of **12**, mp 187–188 °C; IR (KBr) 3000–2870, 1720, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.21 (2 s, 18 H each, 4 *t*-Bu), 1.27 (t, J = 7 Hz, 6 H, 2 CH_2CH_3), 3.98–4.26 (m, 4 H, 2 OCH_2); ^{13}C NMR see Table II. Anal. Calcd for $C_{28}H_{46}O_7$: C, 67.99; H, 9.37. Found: C, 67.98; H, 9.30.

***N,N*-Diethyldipivaloylacetamide (13b).** To a solution of ketene **5** (420 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added diethylamine (140 mg, 2 mmol). After 30 min the solvent was removed by evaporation to yield 560 mg (100%) of **13a**. An analytical sample was prepared by sublimation (90 °C/10^{-1} mbar), mp 156–158 °C; IR (KBr) 3000–2860, 1710, 1700, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16, 1.21 (2 t, J = 7 Hz, 3 H each, 2 CH_2CH_3), 1.20 (s, 18 H, 2 *t*-Bu), 3.12, 3.38 (2 q, J = 7 Hz, 2 H each, 2 NCH_2), 5.44 (s, 1 H, H-2). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.57; H, 10.18; N, 4.70.

***N*-Benzyldipivaloylacetamide (13a).** This compound was prepared analogously to **13b** from **5** and benzylamine (90%): mp 130–132 °C (hexane); IR (KBr) 3340, 3000–2870, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 18 H, 2 *t*-Bu), 4.39 (d, J = 5.5 Hz, 2 H, CH_2), 5.72 (s, 1 H, H-2), 7.12 (br, 1 H, NH), 7.18–7.35 (m, 5 H, Ar-H). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.75; H, 8.51; N, 4.51.

***N*-Phenyldipivaloylacetamide (13c).** To a solution of ketene **5** (210 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (50 mg, 0.5 mmol) and aniline (95 mg, 1 mmol). After 20 h at rt, the solvent was evaporated and the residue digested with cyclohexane. Recrystallization of the crude product from cyclohexane gave 230 mg (75%) of **13c**: mp 141–143 °C; IR (KBr) 3310, 3000–2870, 1720, 1700, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 18 H, 2 *t*-Bu), 5.80 (s, 1 H, H-2), 7.05–7.55 (m, 5 H, Ar-H), 8.68 (br, 1 H, NH). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.34; H, 8.36; N, 4.56.

***S*-Benzyl Dipivaloylthioacetate (14a).** To a solution of ketene **5** (210 mg, 0.5 mmol) and benzylthiol (125 mg, 1 mmol) in CH_2Cl_2 (3 mL) was added triethylamine (ca. 10 mg) as catalyst. After 24 h at rt, the solvent was evaporated and the crude thioester digested with hexane to give 240 mg (72%) of **14a**: mp 96 °C; IR (KBr) 3000–2870, 1725, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 18 H, 2 *t*-Bu), 4.16 (s, 2 H, CH_2), 5.73 (s, 1 H, H-2), 7.28 (s, 5 H, Ar-H). Anal. Calcd for $C_{19}H_{26}O_3S$: C, 68.23; H, 7.84. Found: C, 68.43; H, 7.87.

***S*-(4-Methylphenyl) Dipivaloylthioacetate (14b).** This compound was prepared analogously to **14a** using 4-methylthiophenol as nucleophile (71%): mp 110 °C; IR (KBr) 3000–2870, 1725, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 18 H, 2 *t*-Bu), 2.38 (s, 3 H, Me), 5.81 (s, 1 H, H-2), 7.18 and 7.29 (2 d, J = 8 Hz, 4 H, Ar-H). Anal. Calcd for $C_{19}H_{26}O_3S$: C, 68.23; H, 7.84. Found: C, 68.15; H, 7.76.

Acknowledgment. We gratefully acknowledge financial support by the Austrian Fonds zur Förderung der Wissenschaftlichen Forschung (grant no. P8318-CHE).