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Regioselective Synthesis and Diels−Alder Reaction of 3,4-Dimethylpenta-1,3-diene. Conformational Study of Bicyclic Adducts Structures by ^{1}H NMR (NOESY, ASIS) and Molecular Modeling (MM2, AM1, RHF, and DFT)

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A three-step, regioselective synthesis of 3,4-dimethylpenta-1,3-diene **1** has been developed. The condensation of acetone diethylacetal with ethyl propenyl ether yielded, after hydrolysis of the resulting triethoxy adduct **10**, 2,3-dimethyl-2-butenal **7**. Wittig reaction of **7** with methylenetriphenylphosphorane afforded desired diene **1** in 31% overall yield, easily scalable to the 10 g level. Diels−Alder reaction of **1** with maleic anhydride in benzene was known to afford a 50:50 mixture of "normal" (**2**) and "rearranged" (**3**) adducts. In THF as solvent, **2** has been reproducibly obtained in over 90% yield as a 98:2 mixture with **3**. ^{1}H NMR spectroscopy (NOESY, ASIS) and molecular modeling (MM2, AM1, ab initio) have been used jointly to determine the conformation of **2** and **3**. All are consistent with a *folded* structure of "rearranged" **3**. On the other hand, only RHF/6-31G* and B3LYP/6-31G* ab initio models were in agreement with NMR spectroscopy for an *extended* conformation of adduct **2**. In this case, neither MM2 nor AM1 models gave results consistent with NMR: discrepancies as high as 30° were noted for some dihedrals between these models and ab initio ones.

Introduction

As previously quoted by Chapuis,[1] there are four Diels−Alder approaches to substructure **I** which is common to many fragrances and carotenoids. In particular, when $R_1 = CH_3$, these disconnections relate to the synthesis of Irones which are valuable perfumery compounds isolated from the rhizomes of Iris Pallida.[2] (Figure 1).

The Diels−Alder reaction of 3,4-dimethylpenta-1,3-diene **1** with maleic anhydride is related to disconnection C. In the past, this reaction has given rise to much controversy between several research groups.[3−8] Problems arose mainly from the ease with which diene **1** isomerizes during its Diels−Alder reaction, affording a mixture of adducts **2** and **3** (Scheme 1). This problem was even complicated by the use of mixture of isomers of diene **1**.

Described in this paper is a new synthesis of diene **1** and a long-awaited solution to the univocal synthesis of adduct **2**. An in-depth conformational study of cycloadducts **2** and **3** is also presented.

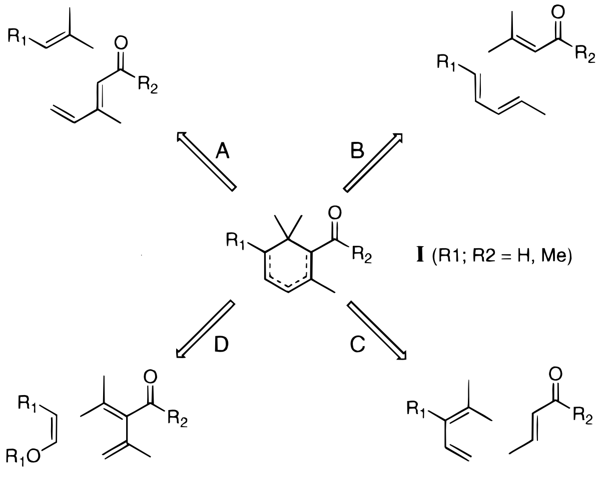
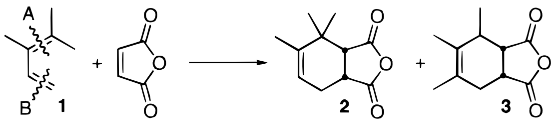


Figure 1. The four Diels−Alder disconnections to **I**.[1]

Scheme 1



Results and Discussion

Synthesis of 3,4-Dimethylpenta-1,3-diene 1. A literature survey showed three syntheses, none of which seemed fully opportune: (i) $KHSO_4$ dehydration of 3,4-dimethylpent-1-en-3-ol[4,9,10] led to a mixture of three isomeric dienes among which desired **1** could only be separated through preparative GC.[5] (ii) Starting with α-acetyl-α-methyl-γ-butyrolactone, Goldman[6] achieved the first unambiguous synthesis of **1**, in five steps with an overall yield of 12%. (iii) Thermal elimination of sulfur

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[1] Chapuis, Ch. *Tetrahedron Lett.* **1991**, *32,* 355.

[2] Ohloff, G. *Scent and Fragrances*; Springer-Verlag: Berlin, Heidelberg, 1994; pp 164−166.

[3] Nazarov, I. N.; Mavrov, M. V. *Doklady Akad. Nauk S.S.S.R.* **1958**, *120,* 86 (*Chem. Abstr.* **1958**, *52,* 20021e).

[4] Nazarov, I. N.; Mavrov, M. V. *Zh. Obshchei Khim.* **1959**, *29,* 1158 (*Chem. Abstr.* **1960**, *54,* 4353i).

[5] Nishida, T.; Arai, A.; Ichikizaki, I. *Bull. Chem. Soc. Jpn.* **1962**, *35,* 572.

[6] Goldman, N. L. *Chem. Ind. (London)* **1963**, *25,* 1036.

[7] Ichikizaki, I.; Arai, A. *Kobayashi Rigaku Ken Kyusho Hokoku* **1963**, *13* (3), 117 (*Chem. Abstr.* **1964**, *61,* 13206g).

[8] Ichikizaki, I.; Arai, A. *Bull. Chem. Soc. Jpn.* **1964**, *37* (3), 432.

[9] Arai, A.; Ichikizaki, I. *Bull. Chem. Soc. Jpn.* **1962**, *35,* 45.

[10] Naves, Y. R.; Ardizio, P. *Helv. Chim. Acta* **1948**, *31,* 2252.

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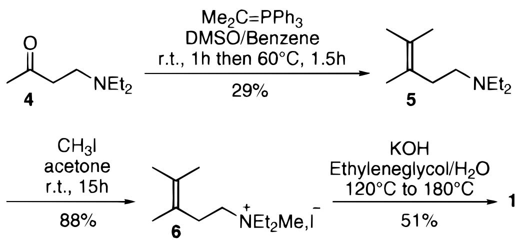
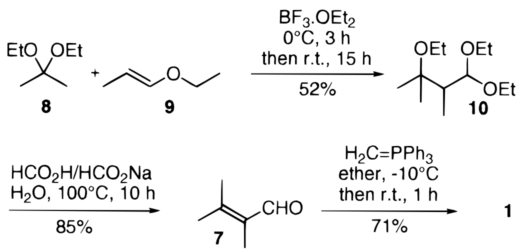
Scheme 2



Scheme 3



dioxide from 2,2,3-trimethyl-2,5-dihydrothiophene 1,1-dioxide in the presence of maleic anhydride resulted in the formation of the "normal" Diels−Alder adduct **2** together with the "rearranged" adduct **3**.[11]

We envisioned the synthesis of **1** through two alternative Wittig disconnections (Scheme 1). First, following disconnection A, Wittig condensation of isopropylidenephosphorane ($^{i}PrP^{+}Ph_3$, I^{-}/*t*-BuOK/ether) on methyl vinyl ketone (MVK) was quickly dismissed because of the instantaneous decomposition of the ketone in the reaction medium. We then turned to the use of a Mannich base equivalent of MVK, commercial 1-(diethylamino)butan-3-one **4** (Scheme 2).

Wittig reaction of aminoketone **4** with the phosphorane (3 equiv) prepared from isopropyltriphenylphosphonium iodide and potassium *tert*-butoxide in DMSO/benzene[12] gave a 29% yield of amine **5**. This low yield probably resulted from the well-known competing enolization of ketones under Wittig conditions, especially with α-disubstituted ylides.[13] No improvements resulted when the described "cyclic regeneration" of the ketone was used.[14] Direct Hofmann degradation[15] of the methiodide **6** derived from **5** afforded smoothly diene **1** in 87% yield (GC determination). However, difficulties in extracting this volatile diene lowered the yield to 51% after elimination of the pentane solvent and distillation. Although shorter than those described, this regioselective synthesis was considered too low-yielding for routine preparation of **1**.

The best synthesis of **1** was achieved following disconnection B (Scheme 1), i.e. by the Wittig reaction between methylenetriphenylphosphorane and 2,3-dimethyl-2-butenal **7**. Among various procedures described[16−19] for the synthesis of this requisite aldehyde **7**, few offer both low cost and effectiveness at a multigram level. Regarding these criterions, the condensation of acetals with enolethers (the Müller-Cunradi/Pieroh process),[20,21] followed by hydrolysis of the resulting 1,1,3-trialkoxyalkanes,[22] seemed suitable. Quite surprisingly, this scheme seemed not to have been already applied to the synthesis of **7**. We then decided to check its efficiency (Scheme 3).

Condensation of 2,2-diethoxypropane **8** with ethyl propenyl ether **9** (both commercially available), afforded 1,1,3-triethoxy-2,3-dimethylbutane **10** in 52% yield after distillation. In this case, the reaction was best catalyzed by boron trifluoride etherate[21] (52% yield) than by the more recently introduced Montmorillonite K10[22] (36% yield). Subsequent treatment of **10** with formic acid/sodium formate[22] gave the desired aldehyde **7** in 85% isolated yield.[19] With aldehyde **7** in hand, we screened several Wittig protocols and found the one of Fitjer and Quabeck[24] particularly suitable for the isolation of volatile material. Following this procedure, diene **1** was isolated in 71% yield after distillation. Up to 16 g of diene **1** was prepared at once using this scheme.

Diels−Alder Reaction of 3,4-Dimethylpentadiene 1 with Maleic Anhydride. As mentioned above, there were discrepancies between authors reporting on the Diels−Alder reaction of 3,4-dimethylpentadiene **1** with maleic anhydride. This cycloaddition was first studied by Nazarov and Mavrov,[3,4] who only obtained the "rearranged" adduct **3** except in one run where "the reason for the failure of **1** to isomerize in this case was not clear". Ichikizaki et al.[5,9] later surmised that Russian authors actually used a mixture of dienes containing large amount of 2,3-dimethylpentadiene **11** which would account for the formation of adduct **3**. Having developed an unambiguous preparation of **1**, Goldman[6] claimed **2** to be the sole adduct of the reaction of **1** with maleic anhydride. However, the debate was not closed because Ichikizaki and Arai[7,8] questioned Goldman's results: starting with pure diene **1**, a mixture of adducts **2** and **3** was again obtained. These authors emphasized that the formation of the "rearranged" adduct **3** "tends to be promoted when air remains in the reaction vessel".[7]

Due to the high potential of adduct **2** in irone syntheses, we decided to revisit this Diels−Alder reaction. Results are summarized in Table 1.

Benzene was used as solvent throughout all previous work in this field.[3−8] In our hands, the reaction in this solvent was slow, even at reflux (entries 1 and 2), affording both adducts in moderate yield. When switching to toluene as solvent (entries 3 and 4), the 30 °C increase in reaction temperature allowed reaction times to be halved. However, with both aromatic solvents, a mixture of adducts is obtained in nonreproducible **2**:**3** ratios ranging from 55:45 to 70:30, respectively (entries 1−4). When ZnI_2 was used as a catalyst,[25] the yield after 1 day

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[11] McIntosh, J. M.; Goodbrand, H. B.; Masse, G. M. *J. Org. Chem.* **1974**, *39*, 202.

[12] Oppolzer, W.; Wylie, R. D. *Helv. Chim. Acta* **1980**, *63*, 1198 and references cited.

[13] Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823 and references cited.

[14] Adlercreutz, P.; Magnusson, G. *Acta Chem. Scand.* **1980**, *B34*, 647.

[15] Julian, P. L.; Meyer, E. W.; Printy, H. C. *J. Am. Chem. Soc.* **1948**, *70*, 887.

[16] Jacobi, P. A.; Brielmann, H. L.; Cann, R. O. *J. Org. Chem.* **1994**, *59*, 5305 and references cited.

[17] Golding, B. T.; Pombo-Villar, E.; Samuel, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1444.

[18] Ono, N.; Miyaka, H.; Tanikaga, R.; Kaji, A. *J. Org. Chem.* **1982**, *47*, 5017.

[19] Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1981**, *4*, 291.

[20] Mueller-Cunradi, M.; Pieroh, K. U.S. Patent 2165962, **1939**; *Chem. Abstr.* **1939**, *33*, 8210.

[21] Hoaglin, R. I.; Hirsh, D. H. *J. Am. Chem. Soc.* **1949**, *71*, 3468.

[22] Fishman, D.; Klug, J. T.; Shani, A. *Synthesis* **1981**, *2*, 137 and references cited.

[23] When the cheaper 2,2-dimethoxypropane was used instead of **8**, a mixture of trialkoxybutanes was obtained which was hydrolyzed directly into aldehyde **7**. In this way, overall yield of aldehyde **7** was slightly lower (44% in lieu of 48%).

[24] Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.

[25] Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299.

Table 1. Diels-Alder Reactions of Diene 1 with Maleic Anhydride

entry	solvent [diene **1**] (mol L^{-1})	maleic anhydride (equiv/**1**)	hydroquinone (equiv/**1**)[a]	temp (°C)	time (h)	% yield[b] **2** + **3**	ratio[c] **2**:**3**
1	benzene (0.25 M)	1.2	0.04	reflux	90	32[e]	35:65 to 50:50
2	benzene (0.25 M)	1.2	0.08	reflux	130	65[e]	35:65 to 50:50
3	toluene (0.25M)	1.2	0.08	reflux	24	48[e]	55:45 to 70:30
4	toluene (0.25M)	1.2	0.08	reflux	65	71[e]	55:45 to 70:30
5	toluene (0.25M)	1.2	0.08 + ZnI_2 (0.3 mol %)	reflux	24	64[e]	0:100
6	benzene (2.1 M)	1.0	0.18	110[d]	10	93	50:50
7	benzene (2.1 M)	1.0	0.18	110[d]	5	93	45:55
8	hexane (2.2 M)	1.0	0.18	100[d]	6	no reaction	-
9	THF (0.1 M)	1.1	0.1	100[d]	24	42[e]	94:6
10	THF (0.1 M)	1.1	0.1	100[d]	72	42[e]	96:4
11	THF (0.1 M)	2.0	0.1	100[d]	24	68[e]	92:8
12	THF (0.1 M)	4.0	0.1	100[d]	24	93	98:2

[a] Polymerization of **1** occurred when hydroquinone was omitted. [b] Isolated combined yield of adducts **2** and **3**. [c] The adduct ratio was determined by the integration of characteristic lines in the 400 MHz ^1H NMR spectrum of the mixture. [d] Schlenk tube. [e] Residual diene **1** was detected in the GC analysis of the crude resultant solution, before the workup.

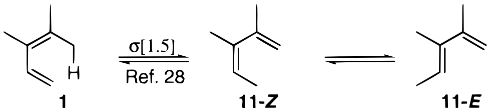
increased from 48% (entry 3) to 64% (entry 5). However, complete isomerization of the diene occurred and only adduct **3** was formed. Under Ichikizaki and Arai's conditions,[7,8] i.e., benzene solution heated for 10h at 110 °C in a Schlenk tube (entry 6), we obtained an equimolar mixture of **2** and **3** in good yield. In fact, the same result could be obtained after only 5 h heating (entry 7).

Having determined the effectiveness of a moderate pressure (ca. 2.5 atm)[26] in this reaction, we next turned to the use of other solvents. No reaction occurred in hexane after 6 h heating at 100 °C (entry 8). Use of THF as solvent (entries 9−12) was quite rewarding. In this solvent, the desired adduct **2** was reproducibly obtained in over 90% yield as a 98:2 mixture with isomer **3** (entry 12).

The reversibility of this reaction is evidenced by the following facts. In the presence of 1.1 equiv of dienophile, extending the reaction time from 24 h to 7 h did not increase the yield of adduct (entries 9 and 10). Only in the presence of 4 equiv of dienophile was a high yield secured. In a control experiment, a mixture of adduct **2** (1 equiv) and maleic anhydride (1 equiv) was heated at 100 °C in THF for 72h. GC analysis of the resulting solution showed a 70:30 proportion between adduct **2** and diene **1** respectively, in good agreement with entry 11 (2 equiv of maleic anhydride).

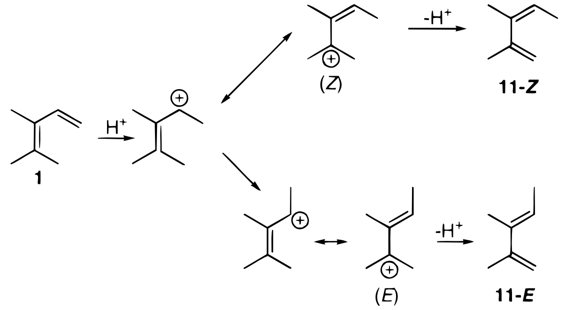
Isomerization of 3,4-Dimethylpenta-1,3-diene 1. Formation of adduct **3** implies an isomerization of diene **1** in an aromatic solvent. A complete thermodynamic study of the [1,5] sigmatropic rearrangement and the cis−trans isomerization of *cis*-2,3-dimethylpenta-1,3-diene were reported by Frey et al.[28] The following equilibria were found to occur in the gas phase between 200 °C and 350 °C (Scheme 4).

Scheme 4



However, though such a mechanism could not be completely ruled out, at least for the [1,5]-sigmatropic shift, catalytic effects most probably promote the rearrangement of diene **1** under Diels−Alder reaction conditions. As a matter of fact, when ZnI_2 (0.3 mol %, Table 1, entry 5) was added in order to accelerate the cycloaddition,[25] complete isomerization of diene **1** occurred first, yielding adduct **3** as the sole product. In other respects, i.e., in the absence of ZnI_2, traces of organic acid could never be completely excluded when using maleic anhydride, which could account for the observed rearrangement in aromatic solvents.[29] Due to its basic character, THF might neutralize these acidic traces, thus preventing diene **1** to isomerize. A plausible pathway could then be as depicted in Scheme 5.

Scheme 5



That maleic anhydride is the vector of these acidic traces (most likely maleic acid) was demonstrated in a control experiment where diene **1**, together with 10 mol % hydroquinone, remained unaffected after 6 h heating at 110 °C in benzene (Schlenk tube).

Conformational Study of Adducts 2 and 3. It was deemed useful to accurately determine the conformations of both **2** and **3** for several reasons: to compare these adducts with similar bicyclic structures which have been described recently by several groups[30,31] and also, in the

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(26) A rough estimation of the pressure inside the sealed tube can be derived from the following equation:[27] $\log_{10} P = 0.05223a/T + b$ where P is the pressure in mm of mercury of the saturated vapor at the absolute temperature T. For benzene: $a = 32295$, $b = 7.6546$ gives $P \cong 2.35$ atms.

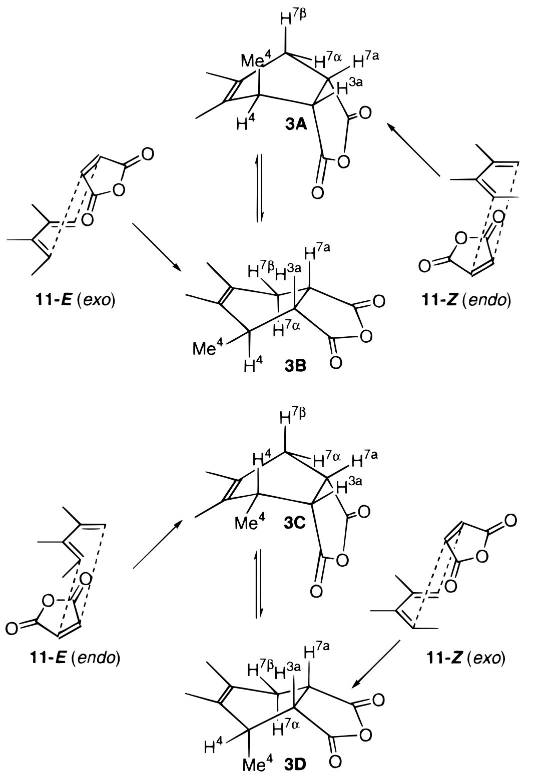
(27) *CRC Handbook of Chemistry and Physics*, 64th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1983−1984; p D-215.

(28) (a) Frey, H. M.; Lamont, A. M.; Walsh, R. *J. Chem. Soc.* (A) **1971**, 2642. (b) One Reviewer drew our attention to a related thermal *Z*:*E* isomerization of a 2-cobalt-substituted-1,3-diene: Wright, M. W.; Welker, M. E. *J. Org. Chem.* **1996**, *61*, 133.

(29) Wollweber, H. *Houben-Weil, Methoden der Organischen Chemie*, 4th ed.; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1970; Vol. V/1c, pp 1067−1068.

(30) See, for instances: (a) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039. (b) Arce, E.; Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421. (c) Boehler, M. A.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 4519. (d) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630. (e) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816. (f) Danishefsky, S.; Kirahara, T. *J. Am. Chem. soc.* **1974**, *96*, 7807.

Scheme 6



case of **3**, to determine under which form *Z* or *E* (Scheme 5) did diene **11** react. Moreover, the question of whether molecular modeling in tandem with the application of Karplus type equations is relevant to the conformational study of flexible bicyclic systems is still in debate.[31] This study was then carried along both experimental (NMR) and theoretical (molecular modeling) sides.

Let us first consider adduct **3**. As diene **11** may react as both *Z* and *E* forms through *endo* or *exo* transition states with maleic anhydride, four adducts should be taken into account. Moreover, as previously quoted by Danishefsky,[31c] each adduct can adopt two boat-type conformations, conveniently described as either *extended* or *folded* forms. However, thanks to symmetry, adducts (*Z-endo*; *E-exo*) on one hand and (*Z-exo*; *E-endo*) on the other hand are mirror images, thus leading to the same diastereomer, respectively. The four possible conformers **3A**−**D** are depicted in Scheme 6.

Although adduct **3** did crystallize from ligroïne-ether, we were unable to obtain single crystals suitable for an X-ray diffraction experiment. We then turned to a NMR study of **3**. First of all, we checked the absence of any conformational equilibrium by low temperature ^{1}H NMR: no peak-broadening was detected, even at 210 K in $CDCl_3$.

The screening of various deuterated solvents showed that a complete separation of all the 400 MHz ^{1}H NMR signals is observed in a 1:1 C_6D_6:$CDCl_3$ mixture.[32] A NOESY experiment was conducted in this solvent mixture and proved to be instructive (Figure 2 and Supporting Information).

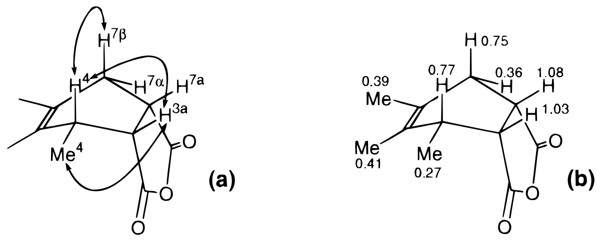


Figure 2. (a) Relevant NOEs observed and (b) ASISs ($\Delta\delta = \delta_{CDCl_3} - \delta_{C_6D_6}$) calculated for adduct **3**.

Strong observed NOEs between $H^{3a}-H^4$ and $H^{3a}-Me^4$ are incompatible with extended structures **3B** and **3D**, respectively, where these groups are in a trans-diaxial arrangement. This leaves folded structures **3A** and **3C** as candidates. However, a moderate transannular NOE is seen between H^4 and one of the H^7 protons. Both should then be axial as in conformer **3C**.

A nice confirmation of this assignment emerged from the aforementioned solvent study. Large (0.75−1.08 ppm) aromatic solvent-induced shifts (ASIS)[33] were indeed observed for H^{3a}, H^4, H^{7a}, and $H^{7\beta}$ when 400 MHz ^{1}H NMR spectra were recorded in $CDCl_3$ then C_6D_6 (Figure 2); knowing that bridgehead protons (H^{3a} and H^{7a}) and the anhydride ring are necessarily anti with respect to the approximate plane comprising carbons 4, 3a, 7a, and 7, it seems reasonable to infer a similar orientation for those protons exhibiting a large ASIS, i.e., H^4 and $H^{7\beta}$. By contrast, 0.25−0.41 ppm ASIS were observed for the remaining syn (or in plane) groups. This particular arrangement can only be found in conformer **3C**. This illustrates that an old and somewhat underappreciated technique could yield interesting results in a simple way. Turning to molecular modeling of the four conformers, we decided to run geometry optimizations at four levels of theory, to gain insight into the reliability of each when applied to such flexible bicyclic structures. Namely, we used MM2,[34] RHF/AM1,[35] RHF/6-31G*,[35] and B3LYP/6-31G*[36] models. Results are summarized in Table 2.

Examination of the four conformers **3A**−**D** revealed that each can be characterized by a set of four J^3_{H-H} coupling constant between $H^{3a}-H^4$, $H^{3a}-H^{7a}$, $H^{7a}-H^{7\alpha}$, and $H^{7a}-H^{7\beta}$. Decoupling (in $CDCl_3$) and COSY (in 1:1 C_6D_6:$CDCl_3$) NMR experiments allowed these key coupling constants to be determined:[32] $J_{3a-4} = 5.77$ Hz, $J_{3a-7a} = 9.86$ Hz, $J_{7a-7\alpha} = 3.82$ Hz, and $J_{7a-7\beta} = 8.10$ Hz. Using dihedral angles resulting from the molecular modeling study, calculated J^3_{H-H} were deduced by application of a Karplus type equation as modified by Bothner-By:[37] $J^3_{H-H} = 10\cos^2\phi - \cos\phi + 2$.

Among various types of the Karplus equations we tried,[31b,38] this one proved to afford the best overall fit.[39] Data collected in Table 2 show that a fair agreement

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[31] (a) Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synthesis* **1998**, *4 Special Issue*, 557. (b) Maddaluno, J.; Gaonac'h, O.; Marcual, A.; Toupet, L.; Giessner-Prettre, C. *J. Org. chem.* **1996**, *61*, 5290. (c) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

[32] Very similar coupling constants were measured in all deuterated solvents tested, namely: $CDCl_3$, C_6D_6 (and 1:1 mixture of these last ones), CD_3OD, and CD_3COCD_3. This proved the solvent-independent conformational stability of adducts **2** and **3**.

[33] Gaudemer, A. *Stereochemistry, Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Thieme Publish.: Stuttgart, ***1977***; Vol. 1, p 102.

[34] CAChe program (V. 3.9 for Powermacintosh): Oxford Molecular, Medawar Center, Oxford Science Park, Oxford, OX4 4GA, England.

[35] MacSpartan Plus (V 1.2 for Powermacintosh): Wavefunction, Inc., 18401 Von Karman Ave., Ste. 370, Irvine, CA 92612.

[36] Gaussian 94, Rev. E2: Gaussian, Inc., Carnegie Office Park, Bldg. 6, Pittsburgh, PA 15106.

[37] Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195.

[38] Balacco, G. *J. Chem. Inf. Comput. Sci.* **1996,** *36*, 885 and references therein.

Table 2. Comparison of Calculated Vicinal H−H Coupling Constants (Hz) of the Four Conformers of 3 with Observed Ones

			MM2			RHF/AM1			RHF/6-31G*			B3LYP/6-31G*		
conformer	protons	J_{obsd}[a]	dihedral (Φ°)	J_{calcd}[b]	ΔJ[c]	dihedral (Φ°)	J_{calcd}[b]	ΔJ[c]	dihedral (Φ°)	J_{calcd}[b]	ΔJ[c]	dihedral (Φ°)	J_{calcd}[b]	ΔJ[c]
3A	3a−4	5.77	−76.16	2.33	3.44	−81.93	2.06	3.71	−75.61	2.37	3.40	−75.94	2.35	3.42
	3a−7a	9.86	−1.49	10.99	−1.13	−0.65	11.00	−1.14	−1.96	10.99	−1.13	−1.27	11.00	−1.14
	7a−7α	3.82	73.27	2.54	1.28	77.97	2.23	1.59	73.15	2.55	1.27	72.73	2.58	1.24
	7a−7β	8.10	−43.78	6.49	1.61	−38.45	7.35	0.75	−41.96	6.79	1.31	−42.10	6.76	1.34
3B	3a−4	5.77	−155.83	11.24	−5.47	−162.24	12.02	−6.25	−154.43	11.04	−5.27	−156.7	11.35	−5.58
	3a−7a	9.86	−13.56	10.48	−0.62	−1.13	11.00	−1.14	−12.32	10.57	−0.71	−10.7	10.67	−0.81
	7a−7α	3.82	168.32	12.57	−8.75	160.22	11.80	−7.98	166.32	12.41	−8.59	166.58	12.43	−8.61
	7a−7β	8.10	50.06	5.48	2.62	43.21	6.58	1.52	49.95	5.50	2.60	50.67	5.38	2.72
3C	3a−4	5.77	52.72	5.06	**0.71**	53.66	4.92	**0.85**	59.76	4.03	**1.74**	59.79	4.03	**1.74**
	3a−7a	9.86	4.06	10.95	**−1.09**	−3.76	10.96	**−1.10**	−1.91	10.99	**−1.13**	−1.40	10.99	**−1.13**
	7a−7α	3.82	65.71	3.28	**0.54**	75.56	2.37	**1.45**	67.74	3.06	**0.76**	67.18	3.12	**0.70**
	7a−7β	8.10	−51.72	5.22	**2.88**	−40.9	6.96	**1.14**	−48.01	5.81	**2.29**	−48.34	5.75	**2.35**
3D	3a−4	5.77	−43.22	6.58	−0.81	−35.52	7.81	−2.04	−43.28	6.57	−0.80	−44.77	6.33	−0.56
	3a−7a	9.86	12.91	10.53	−0.67	2.07	10.99	−1.13	18.40	10.06	−0.20	21.88	9.68	0.18
	7a−7α	3.82	145.93	9.69	−5.87	155.16	11.14	−7.32	139.01	8.45	−4.63	135.23	7.75	−3.93
	7a−7β	8.10	29.65	8.68	−0.58	38.63	7.32	0.78	24.14	9.41	−1.31	21. 07	9.77	−1.67

[a] From decoupling experiments in $CDCl_3$. [b] J calculated according to the following equation:[37] $^3J_{H-H} = 10\cos^2\Phi - \cos\Phi + 2$. [c] $J_{obsd} - J_{calcd}$.

exists between J^3_{H-H} calculated for the folded conformer **3C** and experimental ones, whichever modeling level was used, though the smallest deviations were obtained with the semiempirical AM1 method. This molecular modeling study thus fully supports the previously inferred structure **3C**.

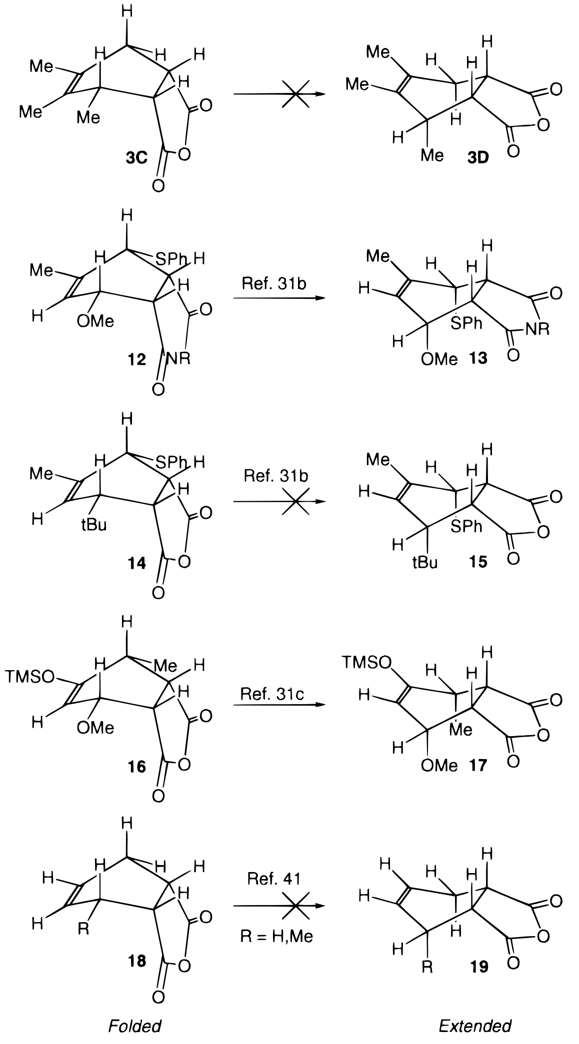
However, there results deserve comments: due to the allylic $A^{1,2}$ strain[40] between methyl groups at C^4 and C,^{5} one could have anticipated extended conformer **3D** to be more stable. Moreover, precedents of such a folded to extended interconversion are known (Scheme 7).

Maddaluno et al.[31b] argued that allylic $A^{1,2}$ strain between the phenylthio and vinylic methyl groups in **12** could force the equilibrium to the extended conformer **13,** thus placing both methoxy and phenylthio substituents in axial positions. However, increasing the steric demand as in **14,** where a *t*-Bu replaced a MeO, apparently obviated the passage to the extended conformer. It is worth emphasizing that conformer **13** is probably further stabilized by favorable electrostatic interactions between O and S atoms.

Such an interconversion was also described 20 years ago by Danishefsky et al.:[31c] folded **16** was less favored than the extended **17**, avoiding the $A^{1,2}$ strain between methyl and trimethylsilyloxy groups but putting both methyl and methoxy groups in a pseudodiaxial orientation. On the other hand, the parent compound was determined to exist preferentially in the folded conformation **18**.[41] Whether a conformation will be more stable than the other seems then to be the result of subtle balance between two unfavorable steric interactions: the $A^{1,2}$ allylic interaction and the syn-1,4-diaxial interaction of substituents borne by the boat cyclohexene ring.

When looking at both RHF/ and B3LYP/6-31G* structures of conformer **3D** (Figure 3), an important deformation of the bicycle become apparent which could be the result of both steric interactions between (i) the axial methyl and the anhydride ring and (ii) the same axial methyl and the syn-axial $H^{7\alpha}$.

Scheme 7



This deformation is clearly reflected by the ab initio calculated dihedral angles $H^{3a}-C^{3a}-C^{7a}-H^{7a}$ of 18.3° (RHF/6-31G*) and 21.8° (B3LYP/6-31G*).

As for conformer **3C**, very little torsional deformation is perceptible: the bridgehead hydrogens form a −1.8° (RHF/6-31G*) and −1.5° (B3LYP/6-31G*) dihedral angle and methyl groups at C^4 and C^5 virtually lie in the same

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(39) Moreover, one of us (P. G.) already described it's successful application to a similar case: Gosselin, P.; Bonfand, E.; Hayes, P.; Retoux, R.; Maignan, C. *Tetrahedron: Asymmetry* **1994**, *5*, 781.

(40) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 738.

(41) Larter, R. M.; Craig, R. E. R.; Craig, A. C.; Mundy, B. P. *J. Org. Chem.* **1977**, *42*, 1259.

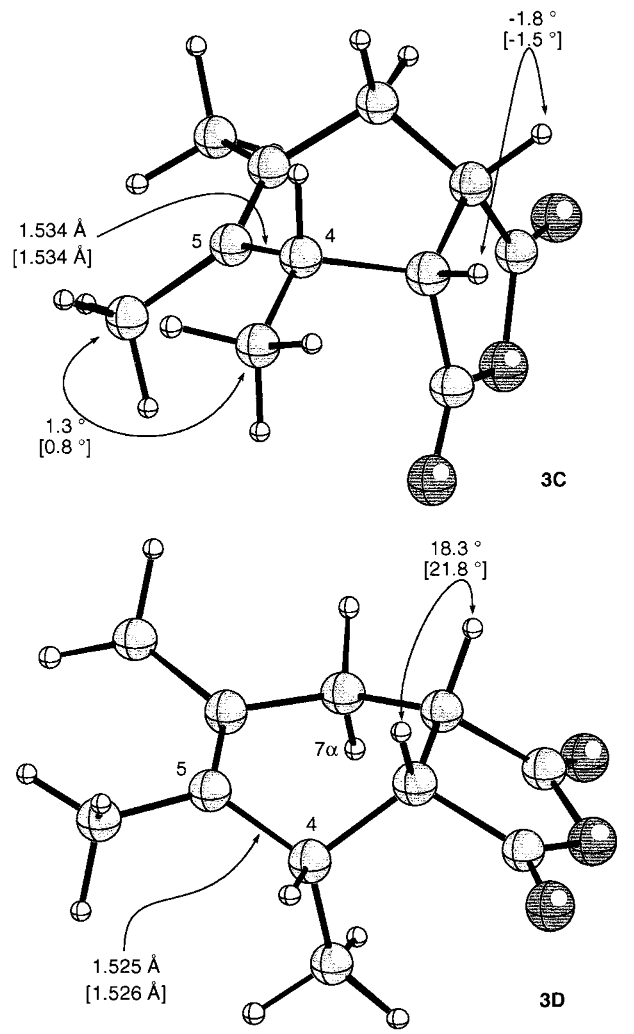


Figure 3. RHF/6-31G* and [B3LYP/6-31G*] calculated models of adducts **3C** and **3D**.

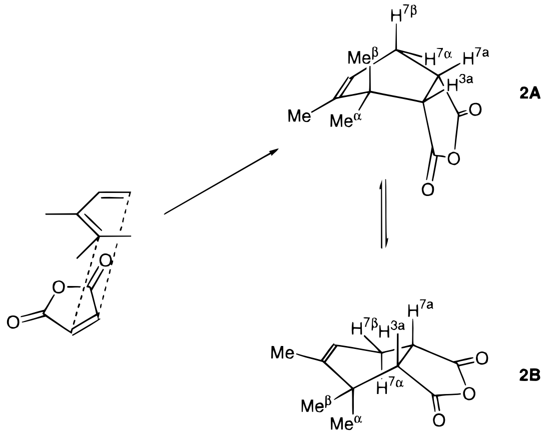
plane with a dihedral angle of 1.3° (RHF/6-31G*) and 0.8° (B3LYP/6-31G*). The allylic interaction seems, however, reflected by a noticeable elongation of the C^4-C^5 single bond: 1.534 Å (both RHF/ and B3LYP/6-31G*) vs 1.525 Å (RHF) and 1.526 Å (B3LYP) for the same bond in conformer **3D**.

It is worth noting that only small conformational energy differences were computed whatever model was used. However, when extended conformer **3D** was preferred over folded **3C** by 0.7 kcal/mol (MM2) or only 0.02 kcal/mol (AM1), both ab initio calculation gave folded **3C** as the most stable conformer by 0.18 kcal/mol (RHF/6-31G*) or 0.45 kcal/mol (B3LYP/6-31G*).

Finally, from a mechanistic point of view, this conformer **3C** may result from either an *endo*-approach of diene **11E** or an *exo*-approach of diene **11Z**, during the Diels–Alder reaction (Scheme 6). *Endo*-approach is the usual rule when considering the cycloaddition of maleic anhydride with alkadienes.[42] This conformational study of adduct **3** then demonstrates that the rearrangement of diene **1** affords diene **11E**.

Following the same steps, we next turned to the conformational study of adduct **2**. According to the aforementioned rule, cycloaddition of diene **1** with maleic anhydride should most probably occur via an *endo*-transition state. However, according to Danishefsky et al.,[31c] "the preference of the *endo* reaction mode in the cycloaddition process need not have any implications of conformational stability of the final product". Thus, we need to consider both folded **2A** and extended **2B** conformers of adduct **2** (Scheme 8).

Scheme 8



Once again, X-ray diffraction was inapplicable, as oily adduct **2** did not crystallize from the numerous solvents we tried. Turning to 400 MHz ^1H NMR, we found acetone-d_6 to induce the largest split between each resonance signals. A NOESY experiment in this solvent strongly supports the extended conformer **2B** (Figure 4).

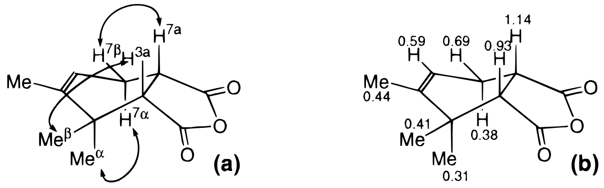


Figure 4. (a) Relevant NOEs observed and (b) ASISs ($\Delta\delta = \delta_{CDCl_3} - \delta_{C_6D_6}$) calculated for adduct **2**.

A much larger NOE was observed between H^{3a} and one of the geminal methyl groups Me^{α}/Me^{β}, and in the same way, only one NOE between H^{7a} and the methylene protons $H^{7\alpha}/H^{7\beta}$. The trans-diaxial arrangement of $H^{3a}-Me^{\alpha}$ and $H^{7a}-H^{7\alpha}$ in the extended conformer **2B** accounts for the absence of NOE between these groups. Considering the folded conformer **2A**, one could have expected NOEs of similar magnitude between H^{3a} and Me^{α}/Me^{β} on one hand and between H^{7a} and $H^{7\alpha}/H^{7\beta}$ on the other hand. This extended conformation is further supported by the observed NOE interaction between Me^{α} and $H^{7\alpha}$, giving evidence for a syn-diaxial arrangement of these protons.

Compared to the folded conformer **3C** studied above, large ASISs are only observed for bridgehead protons H^{3a} and H^{7a}, thus reinforcing the assignment of an extended conformation to adduct **2** (Figure 4). However, an ASIS of 0.69 ppm for $H^{7\beta}$ is still large enough and may indicate some deformation of the boat conformation, which could bring $H^{7\beta}$ and the anhydride ring in a more anti arrangement with respect to the approximate plane comprising carbons 4, 3a, 7a, and 7. This was a further inducement to carry out molecular modeling of both conformers **2A** and **2B**.

Due to long-range couplings, the 400 MHz ^1H NMR spectrum of adduct **2** was somewhat more complicated

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[42] Stephenson, L. M.; Smith, D. E.; Current, S. P. *J. Org. Chem.* **1982**, *47*, 4170 and references therein.

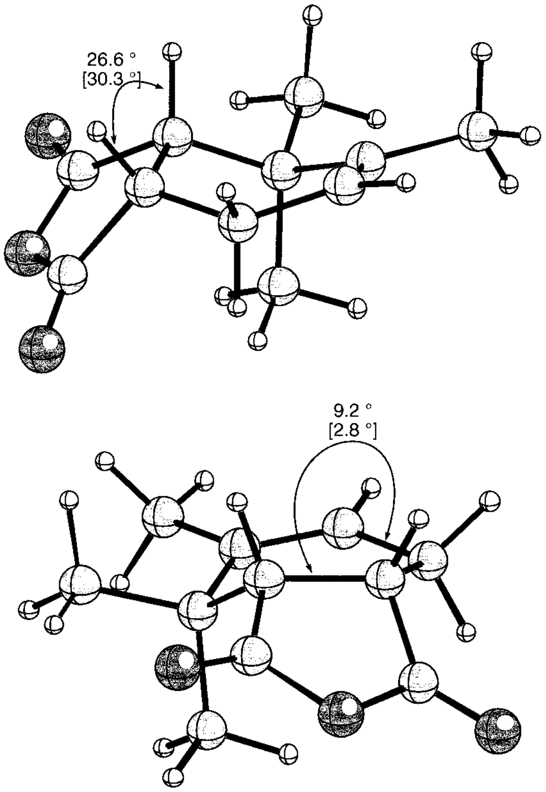

Figure 5. Two views of the RHF/6-31G* and [B3LYP/6-31G*] computed structure of the extended conformer **2B**.

than that obtained with adduct **3**. Decoupling experiments (in acetone-d_6)[32] together with the help of the gNMR software[43] (see Supporting Information) were then used in order to extract all the relevant $J^3_{\mathrm{H-H}}$ coupling constants: $J_{3\mathrm{a}-7\mathrm{a}} = 10.20$ Hz, $J_{7\mathrm{a}-7\alpha} = 5.20$ Hz, $J_{7\mathrm{a}-7\beta} = 10.51$ Hz, $J_{6-7\alpha} = 3.78$ Hz and $J_{6-7\beta} = 5.22$ Hz. As described above for adduct **3**, the Bothner-By equation[37] was used to deduce calculated $J^3_{\mathrm{H-H}}$ between $\mathrm{H}^{3\mathrm{a}}-\mathrm{H}^{7\mathrm{a}}$, $\mathrm{H}^{7\mathrm{a}}-\mathrm{H}^{7\alpha}$, and $\mathrm{H}^{7\mathrm{a}}-\mathrm{H}^{7\beta}$. The Garbish equations[44] were used to compute the vinylic coupling constants between $\mathrm{H}^{6}-\mathrm{H}^{7\alpha}$:

$$J^3_{\mathrm{H-H}} = 6.6\cos^2\phi + 2.6\sin^2\phi\ (0° \le \phi \le 90°)$$

$$J^3_{\mathrm{H-H}} = 11.6\cos^2\phi + 2.6\sin^2\phi\ (180° \ge \phi \ge 90°)$$

From the results reported in Table 3, what is striking is the poor agreement of MM2[34] and AM1[35] calculated coupling constants for either conformers **2A** or **2B** and the excellent one obtained at both RHF/[35] and B3LYP/6-31G*[36] levels for the extended conformer **2B**.

The puckering of the flexible cis-fused bicycle, already suspected from the ASIS study is then fully supported by the sole ab initio calculations. In fact, examination of three relevant dihedral angles disclosed a 30° large distortion within the extended conformer skeleton, when going from the virtually undistorted MM2 and AM1 computed structures to the ab initio ones.

This indicated considerable contortion of the extended boat conformation in the direction of a twist-boat (Figure 5). In particular, the $\mathrm{C}^{3\mathrm{a}}-\mathrm{C}^{7\mathrm{a}}-\mathrm{C}^{7}-\mathrm{C}^{6}$ dihedral angle in **2B** is only 9.2° at RHF/ and 2.8° at B3LYP/6-31G* levels (ca. 37° at either AM1 or MM2 levels).

It is noteworthy that when considering MM2 and AM1 results separately, one could have drawn misleading conclusions from the overall smallest ΔJ found for the folded **2A** conformer. On the other hand, whichever model is considered, vinylic coupling constants deduced from the Garbish equations are more consistent with the extended conformer **2B** ($\Delta J \sim 1$ Hz) than with the folded conformer **2A** ($\Delta J \sim 2.5$ Hz). Such differences are indeed too small to allow for an unambiguous conformational assignment, but these results provide fair support of the assignment.

As compared to the previously studied conformers **3C** and **3D**, greater energetic differences are found here between both conformers: extended **2B** is preferred by 0.55, 0.93, and 1.16 kcal/mol at the AM1, RHF/6-31G*, and B3LYP/6-31G* levels, respectively. The folded **2A** conformer is preferred by 0.15 kcal/mol according to the MM2 calculation.

Conclusions

In summary, through the reevaluation of a useful procedure for preparing enals, we have described a short (three steps, 31% overall yield), regioselective (one diene obtained) synthesis of 3,4-dimethylpenta-1,3-diene **1**, easily applicable at the 10 g level. Provided that the Diels−Alder reaction of **1** with maleic anhydride was effected at 100 °C in THF (Schlenk tube), no isomerization occurred, and thus cycloadduct **2** could be isolated in over 90% yield.

Ready access to quantities of pure adduct **2** opens the way to new efforts in the field of irone syntheses.

A combined NMR and molecular modeling study of adducts **2** and **3**, as representatives of flexible bicyclic systems, allowed for a precise determination of their preferred stereostructures. The hazards of deducing such conformations of bicyclic structures through application of various Karplus relationships have been emphasized in the past;[31] in fact, only the ab initio calculations were able to reveal the considerable distortion of the extended conformer **2B**. Thus, provided that such a high level of calculation is used, molecular modeling *in tandem* with the use of Karplus type relationships are important for studying such flexible bicyclic structures.

Experimental Section

Computational Procedures and Inputs. Molecular modeling was carried out using (i) CAChe Worksystem software[34] for the molecular mechanics calculations ("Augmented" MM2 parameters), (ii) MacSpartan[35] for the semiempirical and ab initio RHF calculations (AM1 and RHF/6-31G*), and (iii) Gaussian 94[36] for the DFT calculations (B3LYP/6-31G*). Identical ab initio optimized structures were obtained, starting from either MM2 or AM1 optimized structures as initial guesses.

General. THF was distilled from Na/benzophenone. Melting points are uncorrected. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C in CDCl$_3$ using TMS for ^{1}H spectra and the solvent for ^{13}C spectra as internal references, unless otherwise noted. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded in KBr dispersion for solids and thin films on NaCl plates for liquids. Mass measurements were obtained by electron impact at 70 eV in an ion trap coupled with a gas chromatograph.

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(43) gNMR (V. 3.6 for Powermacintosh): Cherwell Scientific Publishing Ltd, Magdalen Center, Oxford Science Park, Oxford, OX4 4GA, England.

(44) Garbish, E. W. *J. Am. Chem. Soc.* **1964**, *86*, 5561.

Table 3. Comparison of Calculated Vicinal H−H Coupling Constants (Hz) of the Two Conformers of 2 with Observed Ones

			MM2			RHF/AM1			RHF/6-31G*			B3LYP/6-31G*		
conformer	protons	J_{obsd}[a]	dihedral (Φ°)	J_{calcd}[b]	ΔJ[c]	dihedral (Φ°)	J_{calcd}[b]	ΔJ[c]	dihedral (Φ°)	$J_{calc.}$[b]	ΔJ[c]	dihedral (Φ°)	J_{calcd}[b]	ΔJ[c]
2A (folded)	3a−7a	10.20	−0.97	11.00	−0.80	−1.76	10.99	−0.79	−21.58	9.72	0.48	6.82	10.87	−0.67
	7a−7α	5.20	77.14	2.27	2.93	80.79	2.10	3.10	92.22	2.05	3.15	72.93	2.57	2.63
	7a−7*β*	10.51	−40.25	7.06	3.45	−35.57	7.80	2.71	−22.39	9.62	0.89	−42.59	6.68	3.83
	6−7α	3.78	−25.12	5.88	−2.10	−22.51	6.01	−2.23	−27.74	5.73	−1.95	−21.89	6.04	−2.26
	6−7*β*	5.22	90.67	2.60	2.62	94.78	2.66	2.56	87.97	2.61	2.61	96.24	2.71	2.51
2B (extended)	3a−7a	10.20	1.22	11.00	−0.80	0.97	11.00	−0.80	26.72	9.09	**1.11**	30.30	8.59	**1.61**
	7a−7α	5.20	153.78	10.95	−5.75	154.13	11.00	−5.80	123.90	5.67	**−0.47**	117.37	4.57	**0.63**
	7a−7*β*	10.51	35.85	7.76	2.75	37.29	7.53	2.98	8.71	10.78	**−0.27**	3.02	10.97	**−0.46**
	6−7α	3.78	−93.16	2.63	1.15	−96.83	2.73	1.05	−78.77	2.75	**1.03**	−74.41	2.89	**0.89**
	6−7*β*	5.22	23.35	5.97	−0.75	20.46	6.11	−0.89	36.48	5.19	**0.03**	40.42	4.92	**0.30**

[a] From decoupling experiments in acetone-d_6. [b] J calculated according to the following equations: For 3a−7a, 7a−7a, and 7a−7*β*:[37] $^3J_{H-H} = 10 \cos^2 \Phi - \cos \Phi + 2$; for 6−7α and 6−7*β*:[44] $^3J_{H-H} = 6.6 \cos^2 \Phi + 2.6 \sin^2 \Phi$ ($0° \le \Phi \le 90°$) or $^3J_{H-H} = 11.6 \cos^2 \Phi + 2.6 \sin^2 \Phi$ ($180° \ge \Phi \ge 90°$). [c] $J_{obsd} - J_{calcd}$.

Diethyl(3,4-dimethylpent-3-enyl)amine (5). To a vigorously stirred solution of freshly sublimated tBuOK (6.73 g, 60 mmol, 3 equiv) in DMSO (75 mL) under Ar was added at rt isopropyltriphenylphosphonium iodide[45] (26.9 g, 62.2 mmol, 3.1 equiv). The resulting deep-red solution was stirred for 30 min, and then a solution of 1-(diethylamino)butan-3-one **4** (2.86 g, 20 mmol, 1 equiv) in benzene (75 mL) was added over a 15 min period. The resulting solution was stirred for 1 h at rt then 1.5 h at 60 °C. After cooling to rt, the mixture was poured on half-saturated sodium chloride solution (200 mL) and extracted with pentane (3 × 100 mL). The combined organic extracts were washed with saturated NaCl solution (1 × 150 mL) and then extracted with 5% HCl (3 × 100 mL). The acidic aqueous layer was washed with pentane (1 × 100 mL) and then basified with saturated Na_2CO_3 solution (1 × 100 mL) and extracted with pentane (3 × 100 mL). Drying ($MgSO_4$) and removal of the solvent in vacuo gave **5** (1.0 g, 29.5%) as a pale yellow oil which was used directly in the next step: bp 79−80 °C/20 mmHg; IR (neat) 2971, 2925, 2798, 1679, 1466, 1451, 1381, 1371, 1203, 1177, 1066, 990 cm^{-1}; ^1H NMR δ 1.05 (t, $J = 7.2$ Hz, 6H), 1.64 (s, 3H), 1.66 (br. s, 6H), 2.18 (m, 2H), 2.44 (m, 2H), 2.56 (q, $J = 7.2$ Hz, 4H); ^{13}C NMR δ 11.85 (q, CH_3CH_2N), 18.87, 20.10, 20.55 (3 × q, $CH_3C{=}$), 31.75 (t, CH_2-CH_2N), 46.85 (t, CH_3CH_2N), 50.95 (t, CH_2CH_2N), 124.98 (s, $C{=}$), 125.73 (s, $C{=}$); MS (EI, ion trap) *m*/*z*(%) 170($MH^{+\bullet}$, 3), 87(5), 86($CH_2{=}N^+Et_2$, 100), 58(10).

Diethylmethyl(3,4-dimethylpent-3-enyl)ammonium Iodide (6). To a stirred solution of amine **5** (1.352 g, 8 mmol, 1 equiv) in anhydrous acetone (20 mL) under Ar was added at rt methyl iodide (3.408 g, 1.5 mL, 24 mmol, 3 equiv), via syringe. The mixture was stirred overnight at rt. Removal of solvent and residual methyl iodide in vacuo gave pale-yellow crystals (2.4 g). Recrystallization from ethanol/ether yielded methiodide **6** as white crystals (2.2 g, 88.5%): mp 110−111 °C. Anal. Calcd for $C_{12}H_{26}NI$: C, 46.31; H, 8.42; N, 4.50; I, 40.77. Found: C, 46.25; H, 8.24; N, 4.39; I, 40.50.

1,1,3-Triethoxy-2,3-dimethylbutane (10). Ethyl propenyl ether **9** (51.5 g, 0.6 mol, 1 equiv) was slowly added (≈30 min) under N_2 to a stirred brown mixture of 2,2-diethoxypropane **8** (233 g, 1.77 mol, 3 equiv) and boron trifluoride−etherate (1.2 mL, 9.5 mmol, 0.016 equiv), cooled to −10 °C. Stirring was continued at 0 °C for 3 h and then at rt for 2 h. Powdered K_2CO_3 was then added with stirring until the solution turn orange in color. The reaction mixture was filtered through sintered glass and distilled over K_2CO_3. Unreacted 2,2-diethoxypropane was collected first (91 g, 0.69 mol) followed by 1,1,3-triethoxy-2,3-dimethylbutane **10** (67.7 g, 52%): bp 110−115 °C/110 mmHg; IR (neat) 2975, 2898, 1444, 11374, 1170, 1064, 995 cm^{-1}; ^1H NMR δ 0.95 (d, $J = 7$ Hz, 3H), 1.16 (s, 6H), 1.20 and 1.22 (2t, $J = 7$ Hz, 9H), 1.98 (qd, $J = 7$ Hz and $J = 2$ Hz, 1H), 3.35−3.88 (m, 6H), 4.59 (d, $J = 2$ Hz); ^{13}C NMR δ 8.69, 15.31, 15.49, 16.23, 22.90 and 24.08 (6 q), 44.31 (d), 55.89, 62.91 and 63.16 (3t), 76.19 (s), 104.00 (d).

2,3-Dimethylbut-2-enal (7). 1,1,3-Triethoxy-2,3-dimethylbutane **10** (18.0 g, 0.082 mol, 1 equiv) was slowly added (≈30 min) under N_2 to a refluxing solution of sodium formate (4.21 g, 0.062 mol, 0.75 equiv) in formic acid (15.7 g, 0.34 mol, 4.1 equiv) and water (6.7 g, 0.37 mol, 4.5 equiv). Evolution of the reaction was followed by GC (J&W DB5, 30 m, 50 °C (1 min) and then 200 °C at 10 °C/min); the reflux was then continued for 10 h. After cooling to rt, ice−water (80 g) was added and the aqueous layer extracted with ether (4 × 25 mL). The combined ethereal extracts were washed first with saturated $NaHCO_3$ solution (until basic washings are obtained, ≈3 × 25 mL) and then with saturated NaCl solution (1 × 100 mL) and dried over $MgSO_4$ containing hydroquinone (0.1 g). Ether solvent and ethyl formate were removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure affording 2,3-dimethylbut-2-enal **7** as a colorless oil (6.9 g, 85%): bp 55−60 °C/20 mmHg (lit.:[15] 57−58 °C/20 mmHg); IR (neat) 1673 (C=O), 1638 (C=C), 1456, 1374, 1298, 1163, 1011, 893, 764 cm^{-1}; ^1H NMR δ 1.77, 1.97, 2.20 (3s, 9H), 10.14 (s, 1H); ^{13}C NMR δ 10.77, 19.23, 23.66 (3q), 132.37, 154.86 (2s), 190.93 (d).

3,4-Dimethylpenta-1,3-diene (1). Method A: Starting with Methiodide 6. Methiodide **6** (2.8 g, 9 mmol) was added under N_2 to a stirred solution of KOH (7.5 g, 134 mmol) in ethylene glycol (45 mL) and water (15 mL). The flask was fitted with a thermometer and a distillation apparatus. The temperature of the solution was slowly raised to 125 °C (Bunsen burner) where the reaction began. Heating was continued until the solution reached a temperature of 180 °C. The distillate was then extracted with pentane (3 × 5 mL), washed successively with 5% HCl solution (3 × 5 mL) and saturated $NaHCO_3$ solution (1 × 5 mL), and dried over K_2CO_3. After elimination of the pentane solvent (Vigreux column), diene **1** was distilled to give a colorless oil (0.446 g, 51%). **Method B: Starting with Aldehyde 7.** Methyltriphenylphosphonium bromide (103.6 g, 0.29 mol, 1.1 equiv) was added portionwise, under an Ar stream, to a stirred suspension of freshly sublimated potassium *tert*-butoxide (32.5 g, 0.29 mol, 1.1 equiv) in ether (500 mL). The suspension was refluxed with stirring for 3 h, and then the reflux condenser was replaced by a distillation apparatus and the ether distilled off until the temperature of the remaining slurry reached 45 °C. The mixture was cooled to −10 °C, and 2,3-dimethylbut-2-enal **7** (25.3 g, 0.26 mol, 1 equiv) was added dropwise. The mixture was then allowed to warm to rt and stirring continued for an additional 1 h. Pentane (160 mL) and water (80 mL, ***caution*****: exothermic**) were then successively added. The mixture was then filtered through Celite and the cake thoroughly washed with pentane. The separated aqueous phase was extracted with pentane (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), dried ($MgSO_4$), and filtered, and the pentane/ether solvent was distilled through a 15 cm Vigreux

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(45) Wittig, G.; Wittenberg, D. *Justus Liebig Ann. Chem.* **1957**, *606*, 18.

column. Fractional distillation of the residue afforded 3,4-dimethylpenta-1,3-diene **1** as a colorless oil (16.1 g, 71%): bp 105−110 °C/760 mmHg (lit.:[6] 104−108 °C); IR (neat) 3089, 2971, 1791, 1637 (C═C), 1604 (C═C), 1374, 985 (vinyl), 892 (vinyl) cm^{-1}; ^{1}H NMR δ 1.76, 1.78 and 1.82 (3s, 9H), 4.96 (d, $J = 10.9$ Hz, 1H), 5.09 (d, $J = 17.2$ Hz, 1H), 6.41 (dd, $J = 17.2$ Hz and $J = 10.9$ Hz, 1H); ^{13}C NMR $\delta = 13.73$, 20.38 and 21.98 (3q), 111.02 (t), 126.89 and 131,11 (2s), 136.02 (d).

4,4,5-Trimethyl-3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione (2) (Table 1, entry 12). Diene **1** (5.0 g, 0.052 mol, 1 equiv), maleic anhydride (20.38 g, 0.208 mol, 4 equiv), hydroquinone (0.57 g, 0.0052 mol, 0.1 equiv), and THF (50 mL) were placed into a 100 mL heavy-wall pressure tube. Ar was bubbled through the magnetically stirred solution for a few minutes. The pressure tube was sealed with a Teflon screwing-stopper and heated to 100 °C (oil bath) for 24 h, behind a protective shield. THF was removed in vacuo and the residue heated at 55 °C/0.06 mmHg for 3 h. Most of the remaining maleic anhydride was thus removed. The residue was taken up in $\mathrm{CHCl_3}$ (10 mL) and the precipitated hydroquinone removed by filtration and rinsed with cold $\mathrm{CHCl_3}$ (10 mL). The chloroform solvent was removed in vacuo. The oily residue was freed from traces of maleic anhydride by a last heating at 55 °C/0.06 mmHg for 1 h, affording a 98:2 mixture of adducts **2** and **3,** respectively, as a pale orange oil (9.44 g, 93.5%):[46] IR (neat) 1860 (C═O), 1778 (C═O), 1466, 1221, 1081, 929 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.06 (s, 3H), 1.30 (s, 3H), 1.75 (s, 3H), 2.56 (m, 2H), 2.94 (d, $J = 10.0$ Hz, 1H), 3.37 (dt, $J = 10.0$ and 7.0 Hz, 1H), 5.48 (m, 1H); ^{1}H NMR ($\mathrm{CD_3COCD_3}$) δ 1.06 (s, 3H, Me^{α} on C^4), 1.29 (s, 3H, Me^{β} on C^4), 1.75 (br ddd, $J_{5,6} = 1.65$ Hz, $J_{5,7\alpha} = 2.29$ Hz, $J_{5,7\beta} = 1.70$ Hz, 3H, Me on C^5), 2.41 (m, $J_{7\alpha,7a} = 5.20$ Hz, $J_{7\alpha,7\beta} = -17.67$ Hz, $J_{7\alpha,6} = 3.78$ Hz, $J_{7\alpha,5} = 2.29$ Hz, 1H, $\mathrm{H}^{7\alpha}$), 2.58 (m, $J_{7\beta,7a} = 10.51$ Hz, $J_{7\beta,7\alpha} = -17.67$ Hz, $J_{7\beta,6} = 5.22$ Hz, $J_{7\beta,5} = 1.70$ Hz, 1H, $\mathrm{H}^{7\beta}$), 3.15 (d, $J_{3a,7a} = 10.20$ Hz, 1H, H^{3a}), 3.71 (ddd, $J_{7a,7\beta} = 10.51$ Hz, $J_{7a,7\alpha} = 5.20$ Hz, $J_{7a,3a} = 10.20$ Hz, 1H, H^{7a}), 5.53 (m, $J_{6,7\beta} = 5.22$ Hz, $J_{6,7\alpha} = 3.78$ Hz, $J_{6,5} = 1.65$ Hz, 1H, H^6); ^{13}C NMR ($\mathrm{CDCl_3}$) $\delta = 19.46$, 22.53, 25.56 (3q), 21.39 (t), 36.25 (s), 38.54, 50.97 (2d), 119.44 (d), 141.58 (s), 171.95, 174.14 (2s); MS (EI, 70 eV) *m*/*z*(%) 194 (2, $\mathrm{M}^{+\bullet}$), 166 (22, $(\mathrm{M} - \mathrm{CO})^+$), 151 (6), 121 (27), 107 (100), 91 (33), 79 (12), 65 (7), 41 (14), 28 (43), 18 (33); HRMS calcd for $\mathrm{C_{11}H_{14}O_3}$ 194.09429, found 194.0943.

4,5,6-Trimethyl-3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione (3). According to the same procedure as above for **2** but replacing THF with benzene (Table 1, entry 7), adducts **2** and **3** were obtained as a 45:55 mixture, respectively. Recrystallization from ligroin/ether yielded adduct **3** as a white powder: IR (KBr) 1837 (C═O), 1778 (C═O), 1198, 1057, 964, 911 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.25 (d, $J = 7.4$ Hz, 3H), 1.70 (s, 3H), 1.73 (s, 3H), 2.31 (dd, $J = 15.7$ and 8.1 Hz, 1H), 2.52 (m, 2H), 3.17 (dd, $J = 9.9$ and 5.8 Hz, 1H), 3.30 (m, 1H); ^{1}H NMR (1:1 $\mathrm{C_6D_6}$:$\mathrm{CDCl_3}$) δ 1.06 (d, $J = 7.48$ Hz, 3H, Me on C^4), 1.46 (br s, 3H, Me on C^5), 1.51 (br s, 3H, Me on C^6), 1.85 (br dd, $J_{7\beta,7\alpha} = -15.32$ Hz, $J_{7\beta,7a} = 8.10$ Hz, 1H, $\mathrm{H}^{7\beta}$), 2.05 (br quint, $J_{4,3a} = 5.77$ Hz, $J_{4,\mathrm{Me\ on\ C4}} = 7.48$ Hz, 1H, H^4), 2.26 (br dd, $J_{7\alpha,7a} = 3.57$ Hz, $J_{7\alpha,7\beta} = -15.32$ Hz, 1H, $\mathrm{H}^{7\alpha}$), 2.51 (dd, $J_{3a,4} = 5.77$ Hz, $J_{3a,7a} = 9.78$ Hz, 1H, H^{3a}), 2.59 (ddd, $J_{7a,7\beta} = 8.10$ Hz, $J_{7a,7\alpha} = 3.57$ Hz, $J_{7a,3a} = 9.78$ Hz, 1H, H^{7a}); ^{13}C NMR ($\mathrm{CDCl_3}$) $\delta = 14.34$, 15.68, 19.47 (3q), 29.65 (t), 34.69, 40.22, 45.73 (3d), 126.81, 131.04 (2s), 172.48, 174.71 (2s); MS (EI, 70 eV) *m*/*z* (%) 194 (18, $\mathrm{M}^{+\cdot}$), 166 (20, $(\mathrm{M} - \mathrm{CO})^+$), 151 (5), 121 (53), 107 (100), 91 (39), 81 (16), 65 (11), 53 (12), 39 (24). Anal. Calcd for $\mathrm{C_{11}H_{14}O_3}$: C, 68.02; H, 7.27; O, 24.71. Found: C, 67.97; H, 7.34; O, 24.87.

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Supporting Information Available: The results of gNMR aided determination of coupling constants for compounds **2B** and **3C**, and copies of NOESY ^{1}H NMR spectra (400 MHz) of compounds **2B** and **3C**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(46) Flash chromatography should be avoided because it induced the opening of most of **2** into the corresponding diacid.