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Ruthenium-catalyzed [2+2] cycloadditions between C1-substituted 7-oxanorbornadienes and alkynes

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Abstract—Ruthenium-catalyzed [2+2] cycloadditions between C1-substituted 7-oxanorbornadienes and alkynes were investigated. Most of the cycloadditions occurred smoothly at 65 °C, giving the cyclobutene cycloadducts in moderate to good yields. The C1 substituent showed strong effect on the regioselectivity (up to 110:1) of the cycloadditions.
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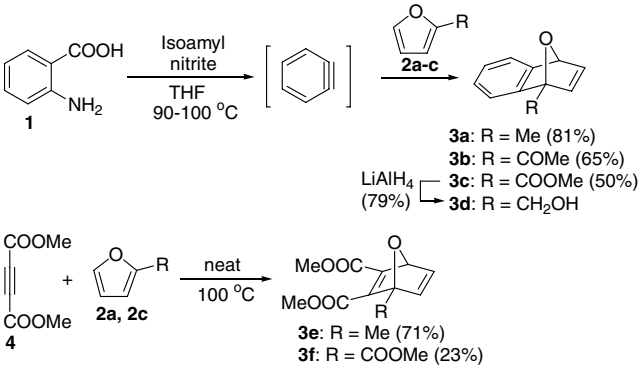
Transition metal-catalyzed cycloadditions have demonstrated their usefulness in the formation of rings and complex molecules.[1] The use of transition metal catalysts provides new opportunities for highly selective cycloaddition reactions since complexation of the metal to an unactivated alkene, alkyne, or diene significantly modifies the reactivity of this moiety, opening the way for enhanced reactivity and novel reactions. Recent developments in transition metal-catalyzed [2+2+1],[2] [4+2],[3] [5+2],[4] [4+4],[5] and [6+2][6] cycloaddition reactions have provided efficient methods for the construction of 5- to 8-membered rings. We and others have studied various aspects of transition metal-catalyzed [2+2] cycloadditions of an alkene and an alkyne for the synthesis of cyclobutenes, including the development of novel catalysts, study of the intramolecular variant of the reaction, investigation of the reactivity of the alkene and the alkyne components in the cycloaddition, and asymmetric induction studies using chiral auxilaries on the alkyne component.[7–11] However, most of the studies employed thus far in transition metal-catalyzed [2+2] cycloadditions employed symmetrical bicyclic alkenes and very little information has been obtained concerning the regioselectivity of the cycloadditions between unsymmetrical bicyclic alkenes and unsymmetrical alkynes. To the best of our knowledge, no study of the Ru-catalyzed [2+2] cycloadditions between C1-substituted bicyclic alkenes and alkynes has been reported in the literature. In this lettter, we report the first examples of ruthenium-catalyzed [2+2] cycloadditions of C1-substituted 7-oxanorbornadienes and various unsymmetrical alkynes.

In order to carry out this study, several C1-substituted 7-oxanorbornadienes were synthesized (Scheme 1). Generation of benzyne from 2-aminobenzoic acid **1** and in situ Diels–Alder reaction with 2-substituted furans **2a–c** provided C1-substituted 7-oxanorbornadienes **3a–c**.[12] Reduction of **3c** with $LiAlH_4$ gave 7-oxanorbornadiene **3d** in 79% yield. 7-Oxanorbornadienes **3e** and **3f** were synthesized by the Diels–Alder reaction between dimethyl acetylenedicarboxylate **4** with 2-substituted furans **2a** and **2c**.[13]



Scheme 1. Synthesis of C1-substituted 7-oxanorbornadienes **3a–f**.

Keywords: Ruthenium; [2+2] Cycloaddition; Cyclobutene; Regioselectivity; Bicyclic alkene; Alkyne.
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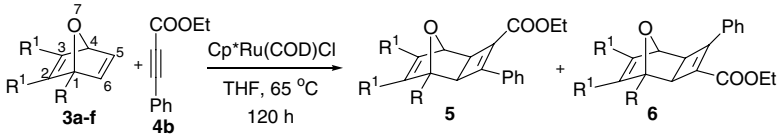
Four different [2+2] cycloadducts are theoretically possible in the cycloaddition between an unsymmetrical bicyclic alkene and an unsymmetrical alkyne (two regioisomers and two stereoisomers). Based on our previous work and others,[8,10] Ru-catalyzed [2+2] cycloadditions between bicyclic alkenes and alkynes usually produced only the *exo*-cycloadducts. Thus, although four possible cycloadducts could be formed, we anticipated that only regioisomers of the *exo*-cycloadducts, **5** and **6**, would be formed in the cycloadditions. When 7-oxabenzonorbornadiene **3a** ($R^1 = -(CH)_4-$, R = Me) and alkyne **4b** were treated with 5 mol % of Cp*RuCl-(COD) in THF at 65 °C for 120 h, a 1:1 mixture of *exo*-regioisomers **5a** and **6a** was obtained in 75% isolated yield (Table 1, entry 1).[14] With 7-oxabenzonorbornadiene **3b** ($R^1 = -(CH)_4-$, $R = CH_2OH$), only 36% of the cycloadducts were isolated (with 60% recovered starting alkyne **4**) but the regioselectivity was improved to 8:1 (entry 2). With a ketone (**3c**, $R = COCH_3$) or an ester (**3d**, R = COOMe) substituent at C1 of the 7-oxabenzonorbornadiene, good yields (82% and 85%, respectively) of the cycloadditions were observed and the regioselectivities were improved further to 66:1 and 76:1 (entries 3 and 4). A similar trend was observed with 7-oxanorbornadienes **3e** and **3f** ($R^1 = COOMe$). With an alkyl C1-substituent (**3e**, R = Me, entry 5), the cycloadducts were produced in 80% yield with a regioselectivity of only 2:1. With an ester C1-substituent (**3f**, R = COOMe, entry 6), the regioselectivity was improved to 99:1. When alkyne **4b** was used as the alkyne component (Table 1, entries 1–6), cycloadduct **5** (with the Ph group closer to the R group) was always the major regioisomer. The structures of regioisomers **5** and **6** were identified by GOESY NMR experiments.[15,16]

Ru-catalyzed [2+2] cycloadditions of 7-oxabenzonorbornadiene **3d** and various alkynes **4a–j** are shown in Table 2. For phenyl acetylenes ($R^2 = Ph$), with $R^3 = a$

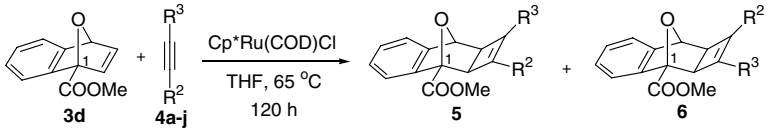
Table 1. Ru-catalyzed [2+2] cycloadditions of 7-oxanorbornadienes **3a–f** and alkyne **4**[a]



Entry	Alkene	R^1	R	Yield[b] (%)	Regioselectivity (**5**:**6**)
1	**3a**	$-(CH)_4-$	Me	75	1:1[c] (**5a**:**6a**)
2	**3b**	$-(CH)_4-$	CH_2OH	36[d]	8:1[c] (**5b**:**6b**)
3	**3c**	$-(CH)_4-$	$COCH_3$	82	66:1[e] (**5c**:**6c**)
4	**3d**	$-(CH)_4-$	COOMe	85	76:1[e] (**5d**:**6d**)
5	**3e**	COOMe	Me	80	2:1[e] (**5e**:**6e**)
6	**3f**	COOMe	COOMe	57	99:1[e] (**5f**:**6f**)

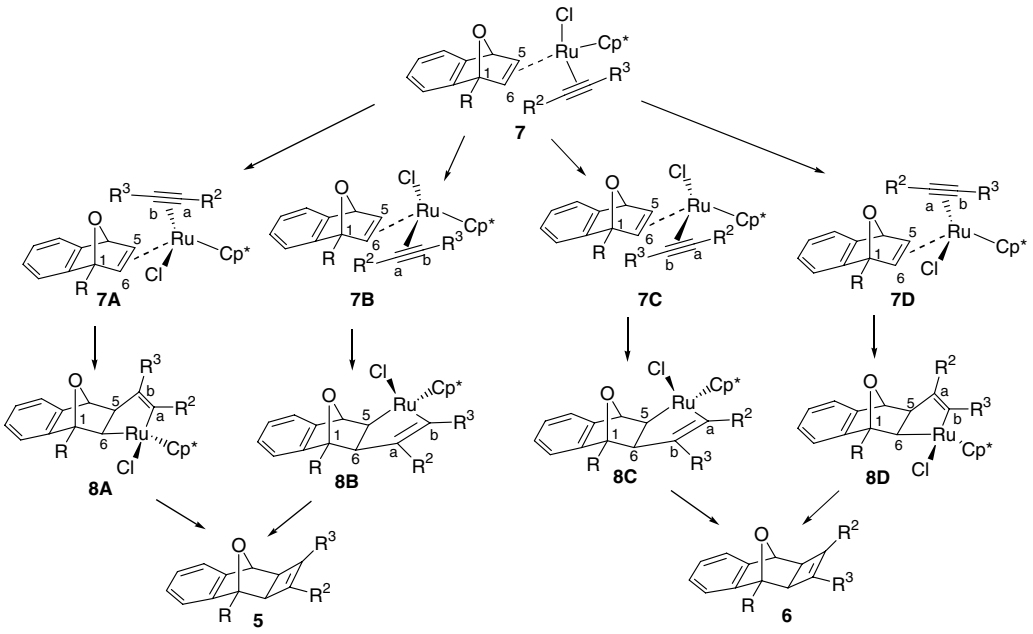
[a] Reaction conditions: alkene **3** (0.3 mmol, 1.25 equiv), alkyne **4** (0.23 mmol, 1 equiv), Cp*Ru(COD)Cl (5 mol %), THF (0.3 mL), 65 °C, 120 h.
[b] Isolated yields after column chromatography.
[c] Measured by ^1H NMR of crude reaction mixture.
[d] Incomplete reaction, 60% of starting alkyne **4** was recovered.
[e] Measured by GC of crude reaction mixture.

Table 2. Ru-catalyzed [2+2] cycloadditions of 7-oxabenzonorbornadiene **3d** and alkynes **4a–j**[a]



Entry	Alkyne	R^2	R^3	Yield[b] (%)	Regioselectivity (**5**:**6**)[c]
1	**4a**	Ph	SO_2Ph	90	110:1 (**5g**:**6g**)
2	**4b**	Ph	COOEt	85	76:1 (**5d**:**6d**)
3	**4c**	Ph	$COCH_3$	90	38:1 (**5h**:**6h**)
4	**4d**	Ph	COOH	56	2.5:1 (**5i**:**6i**)
5	**4e**	Ph	Br	39[d]	1:1.7 (**5j**:**6j**)
6	**4f**	Ph	Me	17[d]	1:4.5 (**5k**:**6k**)
7	**4g**	Ph	CH_2OH	63	1:38 (**5l**:**6l**)
8	**4h**	COOEt	CH_2OH	65	1:39 (**5m**:**6m**)
9	**4i**	COOEt	$C(CH_3)_2OH$	86	1:110 (**5n**:**6n**)
10	**4j**	COOEt	^{n}Bu	87	1:52 (**5o**:**6o**)

[a] Reaction conditions: alkene **3d** (0.3 mmol, 1.25 equiv), alkyne **4** (0.23 mmol, 1 equiv), Cp*Ru(COD)Cl (5 mol %), THF (0.3 mL), 65 °C, 120 h.
[b] Isolated yields after column chromatography.
[c] Measured by GC of crude reaction mixture.
[d] Incomplete reaction, starting alkyne **4** was recovered.



Scheme 2. Proposed mechanism.

sulfone, an ester, a ketone or a carboxylic acid (entries 1–4), cycloadduct **5** (with the Ph group closer to the C1 COOMe group) was formed as the major regioisomer. Alkynyl sulfone gave the highest regioselectivity of 110:1 (entry 1), followed by alkynyl ester (76:1, entry 2) and alkynyl ketone (38:1, entry 3). Alkynyl carboxylic acid gave the lowest regioselectivity of 2.5:1 (entry 4). On the other hand, for phenyl acetylenes ($R^2 = Ph$), with R^3 = a bromide, a methyl group and a propargylic alcohol (entries 5–7), cycloadduct **6** (with the Ph group further away from the C1 COOMe group) was formed as the major regioisomer. While alkynes **4e** and **4f** gave low regioselectivities (entries 5 and 6), propargylic alcohol **4g** gave a good regioselectivity of 38:1 in favor of cycloadduct **6**. When R^2 = COOEt (entries 8–10), both primary and tertiary propargylic alcohols (**4h** and **4i**) as well as alkyne **4j** (with $R^3 = {}^n$Bu) gave excellent regioselectivities and cycloadduct **6** was formed as the major regioisomer.

Upon complexation of an unsymmetrical C1-substituted 7-oxanorbornadiene **3** and alkyne **4** with the Ru catalyst to give **7** (Scheme 2), four different metallacyclopentenes **8A**–**D** could be formed. Carbon–carbon bond formation may first occur between the acetylenic carbon attached to the R^3 group (C-b) with one of the olefinic carbons of 7-oxanorbornadiene **3** (C-5 or C-6) to give **8A** or **8C**. Alternatively, formation of the carbon–carbon bond between the acetylenic carbon attached to the R^2 group (C-a) with one of the olefinic carbons of 7-oxanorbornadiene **3** (C-5 or C-6) will give **8B** or **8D**. In **8A** and **8D**, the carbon–ruthenium bond is closer to the C1 substituent (R group) whereas in **8B** and **8C** the carbon–ruthenium bond is farther away from the C1 substituent (R group). Reductive elimination of metallacyclopentenes **8A** and **8B** would lead to the formation of regioisomer **5** whereas reductive elimination of metallacyclopentenes **8C** and **8D** would lead to the formation of the minor regioisomer **6**. Although at the present stage, it is difficult to explain all the trends and selectivities in Tables 1 and 2, several characteristics can be noted. When the C1 substituent is a nonchelating group (e.g., a Me group, Table 1, entries 1 and 5), the regioselectivities of the cycloadditions were very low (1:1 to 2:1). However, when the C1-Me group is replaced by a group that is capable of coordination (e.g. a propargylic alcohol, a ketone and an ester, Table 1, entries 2–4 and 6) with the Ru, the regioselectivity increased dramatically. Similar trends were observed for the cycloadditions between 7-oxanorbornadiene **3d** and various alkynes (Table 2). When the alkynes contain groups that are capable of coordination with the Ru, the regioselectivities are generally very high. For alkynes that are incapable of coordinating with the Ru (e.g., alkynes **4e** and **4f**, Table 2, entries 5 and 6), the regioselectivities of the cycloadditions were much lower. The exact nature of the stereoelectronic effect of the C1 substituent is still not certain at this stage and further investigations, including molecular modeling studies on the relative stability of different metallacyclopentenes **8A**–**D** and the energy profile of each reaction pathway, are ongoing in our laboratory.

In conclusion, we have studied the first examples of the effect of a C1 substituent of 7-oxanorbornadienes on the regioselectivity of ruthenium-catalyzed [2+2] cycloadditions with various unsymmetrical alkynes. The cycloadditions occurred smoothly at 65 °C, giving the *exo*-cycloadducts in moderate to good yields. Regioselectivities of 1:1 to 110:1 were observed. Further investigation on the mechanism of the cycloaddition and the role of the C1 substituent on the regioselectivity of the cycloaddition, as well as investigations on the use of the cycloadducts for the synthesis of more complex polycyclic natural products is currently in progress in our laboratory.

Acknowledgements

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14. *General procedure for ruthenium-catalyzed [2+2] cycloadditions*: A mixture of a 1-substituted oxabicyclic alkene (0.29 mmol, 1.25 equiv), an alkyne (0.23 mmol, 1 equiv) and dry THF (0.3 mL) in an oven-dried vial was added via a cannula to an oven-dried screw-cap vial containing Cp*RuCl(COD) (weighed out from a dry box, 0.012 mmol, 5 mol %) under nitrogen. The reaction mixture was stirred in the dark at 65 °C for 120 h. The crude product was purified by column chromatography (EtOAc–hexanes mixtures or CH_2Cl_2) to give the cycloadducts. Regioselectivity was based on the crude ^1H NMR spectra and/or GC analysis of the crude product. The structures of the regioisomers were determined by 1D GOESY (Gradient Nuclear Overhauser Effect Spectroscopy) NMR Experiments.
Cycloadducts **5a** (Table 1, entry 1): R_f 0.44 (EtOAc–hexanes = 2:8); mp 135–138 °C; IR (CH_2Cl_2) ν_{max} (cm^{-1}) 3070(w), 2977(m), 1702(s), 1616(m), 1492(m), 1447(m), 1332(w), 1288(m), 1216(s), 1181(s), 1122(m), 1042(m); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (m, 2H), 7.42 (m, 4H), 7.26 (m, 3H), 5.20 (s, 1H), 4.33 (q, 2H, $J = 7.1$ Hz), 3.01 (d, 1H, $J = 3.6$ Hz), 2.98 (d, 1H, $J = 3.6$ Hz), 1.64 (s, 3H), 1.40 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz): 162.6, 154.8, 147.3, 145.3, 132.7, 130.2, 129.3, 128.9, 128.2, 126.8(2), 119.8, 118.4, 82.8, 76.3, 60.4, 47.10, 47.06, 15.6, 14.4. HRMS (EI) calcd. for $C_{22}H_{20}O_3$ (M^+): 332.1412; found: 332.1417.
Cycloadducts **6a** (Table 1, entry 1): R_f 0.43 (EtOAc–hexanes = 2:8); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.13 (m, 2H), 7.46 (m, 3H), 7.34 (m, 1H), 7.25 (m, 3H), 5.13 (s, 1H), 4.36 (q, 1H, $J = 7.1$ Hz), 4.29 (q, 1H, $J = 7.1$ Hz), 3.10 (d, 1H, $J = 3.6$ Hz), 2.87 (d, 1H, $J = 3.6$ Hz), 1.84 (s, 3H), 1.40 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz): δ 162.9, 155.8, 147.5, 145.2, 131.9, 130.4, 129.1, 128.4, 128.0, 126.9, 126.6, 119.4, 118.8, 83.1, 76.0, 60.3, 47.5, 46.8, 15.0, 14.3. HRMS (EI) calcd. for $C_{22}H_{20}O_3$ (M^+): 332.1412; found: 332.1419.
Cycloadducts **5e** and **6e** (Table 1, entry 5): Inseparable 2:1 mixture. GC (HP-1 column) retention time of major isomer **5e** is 32.702 min and retention time of minor isomer **6e** is 33.115 min; IR (CH_2Cl_2) ν_{max} (cm^{-1}) 2983(m), 2954(m), 1713(s), 1625(m), 1492(m), 1436(m), 1387(m), 1368(m), 1329(s), 1299(s), 1249(s), 1216(s), 1183(s), 1112(m), 1062(m); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.08 (m, 0.66H), 8.01 (m, 1.33H), 7.41 (m, 3H), 5.04 (s, 0.66H), 5.01 (s, 0.33H), 4.29 (m, 2H), 3.88 (s, 3H), 3.84 (s, 1H), 3.83 (s, 2H), 3.26 (d, 0.66H, $J = 3.6$ Hz), 3.20 (d, 0.33H, $J = 3.6$ Hz), 3.11 (d, 0.33H, $J = 3.6$ Hz), 3.08 (d, 0.66H, $J = 3.6$ Hz), 1.66 (s, 1H), 1.48 (s, 2H), 1.36 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz): major isomer **5e** δ 164.5, 162.3, 162.6, 154.5, 147.2, 141.9, 132.3, 130.5, 129.2, 128.8, 128.3, 86.7, 77.2, 60.4, 52.4(2), 45.3, 45.2, 15.2, 14.31; visible peaks for minor isomer **6e:** δ 155.9, 148.4, 140.4, 131.3, 130.7, 129.0, 128.5, 127.6, 87.2, 76.9, 45.6, 45.1, 14.5, 14.26. Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.47; H, 5.20.
Cycloadducts **5f** (Table 1, entry 6): R_f 0.45 (EtOAc–hexanes = 4:6); mp 149–150 °C; IR (CH_2Cl_2) ν_{max} (cm^{-1})

2955(m), 1743(s), 1628(m), 1494(w), 1437(m), 1326(m), 1260(m), 1214(m), 1185(m), 1149(m), 1077(m), 1055(m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (m, 2H), 7.38 (m, 3H), 5.19 (s, 1H), 4.31 (q, 1H, $J = 7.1$ Hz), 4.30 (q, 1H, $J = 7.1$ Hz), 3.93 (s, 3H), 3.82 (s, 3H), 3.69 (d, 1H, $J = 3.6$ Hz), 3.39 (s, 3H), 3.14 (d, 1H, $J = 3.6$ Hz), 1.38 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz): δ 166.4, 163.9, 162.0, 161.4, 152.9, 146.6, 138.2, 131.1, 130.8, 129.0, 128.8, 128.3, 87.4, 76.9, 60.7, 52.9, 52.6, 52.5, 46.1, 44.0, 14.3. Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01. Found: C, 62.76; H, 4.88.

Cycloadducts **5g** (Table 2, entry 1): R_f 0.45 (EtOAc–hexanes = 4:6); mp 158–161 °C; IR (CH_2Cl_2) ν_{max} (cm^{-1}) 3065(w), 3006(w), 2952(w), 1762(m), 1736(m), 1608(m), 1491(w), 1446(m), 1306(s), 1197(m), 1152(s), 1108(m), 1087(m), 1059(w); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, 2H, $J = 7.4$ Hz), 7.90 (m, 2H), 7.57 (m, 4H), 7.43 (m, 3H), 7.27 (m, 3H), 5.12 (s, 1H), 3.48 (s, 3H), 3.44 (d, 1H, $J = 3.5$ Hz), 3.00 (d, 1H, $J = 3.5$ Hz); ^{13}C NMR (APT, $CDCl_3$, 100 MHz): δ 168.1, 152.3, 142.9, 141.7, 140.7, 133.8, 133.5, 131.2, 130.0, 129.4(2), 128.6, 128.0, 127.4(2), 120.21, 120.16, 83.6, 76.1, 52.1, 48.1, 47.6. Anal. Calcd for $C_{26}H_{20}O_5S$: C, 70.25; H, 4.54. Found: C, 70.42; H, 4.40.

Cycloadducts **6n** (Table 2, entry 9): R_f 0.33 (EtOAc–hexanes = 4:6); mp 117–120 °C; IR (CH_2Cl_2) ν_{max} (cm^{-1}) 3516(m), 3424(m), 2978(m), 1762(s), 1711(s), 1644(m), 1458(m), 1440(m), 1370(m), 1324(s), 1253(s), 1194(s), 1111(m), 1064(m), 1033(m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (dm, 1H, $J = 7.0$ Hz), 7.37 (dm, 1H, $J = 7.0$ Hz), 7.26 (m, 2H), 5.23 (s, 1H), 4.76 (s, 1H), 4.29 (m, 2H), 3.94 (s, 3H), 3.12 (d, 1H, $J = 3.4$ Hz), 2.83 (d, 1H, $J = 3.4$ Hz), 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz): δ 168.7(2), 162.9, 143.4, 142.2, 129.2, 127.9, 127.1, 119.9, 119.8, 83.8, 76.1, 70.3, 61.1, 52.5, 48.2, 45.7, 28.7, 26.9, 14.2. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.36; H, 6.02.

15. GOESY: Gradient enhanced nuclear Overhauser enhancement spectroscopy, see: (a) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037; (b) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199; (c) Dixon, A. M.; Widmalm, G.; Bull, T. E. *J. Magn. Reson.* **2000**, *147*, 266.
16. For determination of *exo* and *endo* stereochemistry of [2+2] cycloadducts, see our previous work in Ref. 10.