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Useful Enantioselective Bicyclization Reactions Using an N-Protonated Chiral Oxazaborolidine as Catalyst

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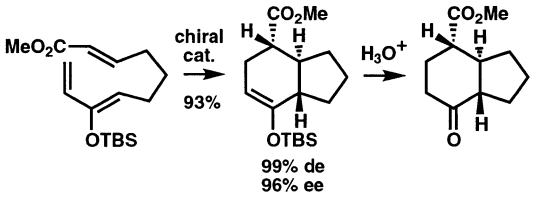
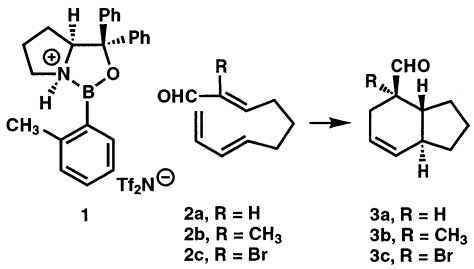
ABSTRACT



Nine examples are reported of enantioselective [4 + 2] cycloaddition reactions of achiral, acyclic substrates to form chiral bicyclo[4.3.0]-nonane or bicyclo[4.4.0]decane derivatives.

N-Protonated oxazaborolidines such as **1** are outstandingly powerful and useful cationic chiral catalysts for intermolecular enantioselective Diels−Alder reactions with achiral substrates.[1−4] Because of their potency, these catalysts effect highly enantioselective reactions between a wide range of dienes and dienophiles, including both acyclic and cyclic dienes, α,β-enals, α,β-enones, α,β-unsaturated lactones, 1,4-benzoquinones, and 1,4-benzoquinone monoketals. The mechanistic model[5,6] for these reactions allows the prediction of the absolute stereochemistry of reaction products, another useful aspect of this methodology. This paper deals with the first application of N-protonated oxazaborolidine **1** to enantioselective intramolecular Diels−Alder reactions with achiral α,β-unsaturated aldehyde/1,3-diene and α,β-unsaturated ester/1,3-diene derivatives as reactants. The literature reports two instances of such a reaction with a chiral catalyst, the conversion **2a** → **3a** in 46% ee and 80% ee and **2b** → **3b** in 84% yield and 92% ee.[7−9]



The intramolecular Diels−Alder reaction of the trienal **2b**[8] took place smoothly in the presence of 0.2 equiv of catalyst

(1) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808−3809.

(2) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993.

(3) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390.

(4) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

(5) For α,β-enals, this model[1] involves formyl C−H- -O hydrogen bonding and π−π attractive interaction between the coordinated α,β-enal and the proximate C-aryl substituent in **1**. See: Corey E. J.; Lee, T. W. *J. Chem. Soc., Chem. Commun.* **2001**, 1321−1329.

(6) For α,β-unsaturated esters, lactones, and ketones with an α-C−H unit, the model[2] involves α-C−H- -O hydrogen bonding and π−π attractive interaction between the coordinated dienophile and the proximate C-aryl substituent in **1**.

(7) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049−3050.

(8) Furuta, K.; Kanemitsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231−7232.

(9) In addition, several examples have been recorded of catalytic enantioselective intramolecular Diels−Alder reactions with *N*-acyloxazolidinone/trienes as reactants. See: (a) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947−1950. (b) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787.

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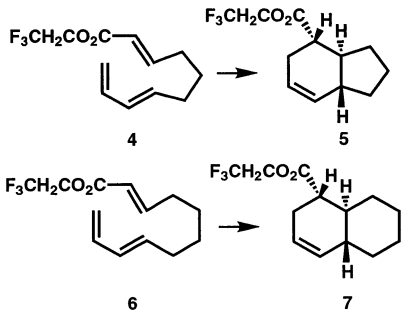
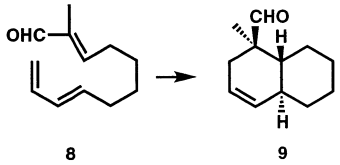
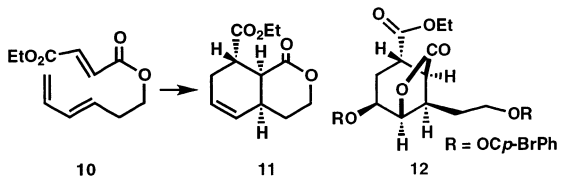
1 in CH_2Cl_2 at −78 °C after 4.5 days to give 93% yield of the endo product **3b** in 98% de and 90% ee.[10] The corresponding reaction occurred with the α-bromo trienal **2c** (0.2 equiv of catalyst **1** in CH_2Cl_2 at −78 °C for 3 days) to afford the endo product **3c** in 98% de and 94% ee,[11] $[\alpha]^{23}_D$ +136.3 (c = 0.95, $CHCl_3$).



α,β-Unsaturated esters are much less reactive in Lewis acid catalyzed Diels−Alder reactions than the corresponding α,β-unsaturated aldehydes, and this is probably why no examples of efficient catalytic enantioselective intramolecular reactions of this type appear in the literature.[12] Nonetheless, reaction of the triene ester **4** with 0.2 equiv of **1** (no solvent) at 35 °C for 10 h resulted in formation of Diels−Alder adduct **5** in 75% yield (along with 20% of unchanged **4**) in 98% de and 93% ee.[13] The results of this experiment are noteworthy not only because this represents the first example of a highly enantioselective Diels−Alder reaction of a triene ester but also because the absolute stereochemical course of the reaction is that predicted by the model.[6] Although the corresponding intramolecular Diels−Alder reaction of the higher homologue **6** is also highly enantioselective under the same conditions used for **4** → **5**, to form **7** in 92% ee, the reaction is considerably slower (with 0.2 equiv of **1** as catalyst at 40 °C and with no solvent) and affords 41% yield of **7** along with 45% of recovered **6**.[14] The lower rate of intramolecular [4 + 2] cycloaddition leading to 6/6-fused ring products as compared to the corresponding 6/5-fused structures (which also is apparent in previous studies)[12b,14] appears to be due to the less favorable [4 + 2] cycloaddition stereoelectronics for 6/6-fused ring formation. It is interesting in this connection that the intramolecular Diels−Alder reaction of **8** to form **9** not only proceeds slowly relative to **2b** → **3b** (using 0.2 equiv of **1**, no solvent, at −45 °C for 2 days) but also less stereoselectively (90% yield, 2:1 endo/exo selectivity, 80% ee for **9** and 89% ee for the exo diastereomer).[15]



The mixed ester, ethyl *E*-3,5-hexadienyl fumarate (**10**), underwent intramolecular [4 + 2] cycloaddition (0.2 equiv of **1**, no solvent, 40 °C, 12 h) to afford the bicyclic lactone **11** in 71% yield (along with 10% recovered **10**) with complete diastereoselectivity and with 86% ee; $[\alpha]^{23}_D$ −50 (c = 0.6, $CHCl_3$).[16] The absolute and relative configurations



of **11** were established by conversion of **11** to lactone triester **12** by the sequence: (1) dihydroxylation of the olefinic linkage of **11** with OsO_4−*N*-methylmorpholine *N*-oxide in acetone−H_2O and chromatographic purification of the resulting diol and (2) concurrent translactonization and esterification by reaction with *p*-bromobenzoyl chloride in pyridine

(10) The exo/endo ratio and the enantioselectivity were determined for **3b** by GC analysis using a J&W Scientific Cyclosil-B column (30 m × 0.25 mm, 100 °C, 25 psi); retention times: 32.60 min (endo, major, 31.95 min (endo, minor), 26.75 min (exo isomer), 23.35 min (exo isomer). The absolute configuration was determined by comparison of optical rotation with the known adduct,[8] $[\alpha]^{20}_D$ +10 (c = 1.06, $CHCl_3$).

(11) Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, $CDCl_3$): δ 3.57 (s, MeO, 3H, minor, 3.55 (s, MeO, 3H, major; ^{19}F NMR integration (376.2 MHz, $CDCl_3$): δ −71.79 (s, CF_3, major), −71.89 (s, CF_3, minor). The absolute configuration of adduct **3c** follows from its high dextrorotation ($[\alpha]^{23}_D$ +136) by application of the confirmational preference/α-bromocarbonyl correlation (see, Corey, E. J.; Ursprung, J. J. *J. Am. Chem. Soc*. **1955**, *77*, 3667−3668), from analogy with **3b**, and from the mechanistic model.[5]

(12) See, for example: (a) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc*. **1982**, *104*, 2269−2283. (b) Wullf, W. D.; Powers, T. S. *J. Org. Chem*. **1993**, *58*, 2381−2393.

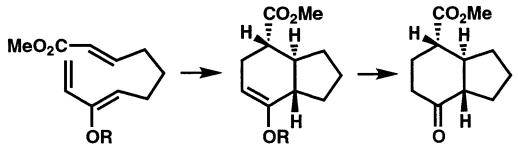
(13) The relative configuration for **5** was determined from ^{1}H NMR NOE data. The exo/endo ratio was determined by GC analysis using a J&W Scientific Cyclosil-B column (30 m × 0.25 mm, 100 °C, 25 psi); retention times: 18.4 min (endo, major) 23.2 min (exo, minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, $CDCl_3$): δ 4.13 (dd, 1H, J = 11.0, 4.5 Hz, major), 4.38 (dd, 1H, J = 11.0, 4.5 Hz, minor). The absolute configuration was determined from the rotation of the known[12] corresponding alcohol, $[\alpha]^{23}_D$ +38 (c = 1.00, $CHCl_3$).

(14) The relative configuration for **7** was determined from ^{1}H NMR NOE data. The exo/endo ratio was determined by GC analysis using a J&W Scientific Cyclosil-B column (30 m × 0.25 mm, 120 °C, 25 psi); retention times: 16.1 min (endo, major), 17.2 min (exo, minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration (500 MHz, $CDCl_3$): δ 4.30 (dd, 1H, J = 10.5, 3.5 Hz, major), 4.24 (dd, 1H, J = 10.5, 3.5 Hz, minor). The absolute configuration was determined by conversion of the Diels−Alder adduct to the known benzyl ester with lithium benzyl oxide and measurement of optical rotation, $[\alpha]^{23}_D$ +6.9 (c = 1.00, $CHCl_3$); see, Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.

(15) The *exo*/*endo* ratio and the enantioselectivity were determined by GC analysis using a J&W Scientific Cyclosil-B column (30 m × 0.25 mm, 120 °C, 25 psi), retention times: 21.99 min (exo, minor), 25.00 min (exo, major), 27.33 min (endo, minor), 28.28 min (endo, major). The absolute configuration of **9** was assigned by analogy with **3b** and **3c**.

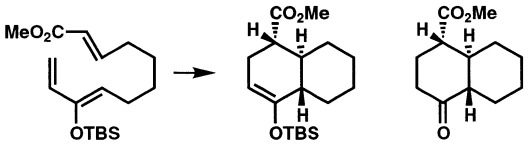
(16) Diastereoselectivity was determined by ^{1}H NMR analysis and relative configuration was deduced from NOE data. Enantioselectivity were determined by GC analysis of the partly reduced product using a J&W Scientific Cyclosil-B column (30 m × 0.25 mm, 130 °C, 25 psi, retention times: 23.9 min (endo, major), 24.6 min (endo, minor). The formation of **11** from **10** can be understood in terms of an exo-COOEt selectivity in the [4 + 2] cycloaddition (with **1** coordinating to the COOEt group). The same diastereoselectivity has been noted for the Et_2AlCl-catalyzed cyclization of **10** by: Chen, C.-Y.; Hart; D. J. *J. Org. Chem.* **1993**, *58*, 3840−3849.

containing 4-(dimethylamino)pyridine at 23 °C for 24 h, (3) recrystallization of **12** from hexane-benzene (10:1), and (4) single-crystal X-ray analysis which revealed the absolute structure as **12**. The three-step synthesis of the bridged-ring lactone **12** from the achiral precursor with the creation of two rings and five stereocenters provides one illustration of the power of the enantioselective methodology based on the chiral catalyst **1**.



13a, R = *t*-BuMe$_2$Si
13b, R = *i*-Pr$_3$Si
14a, R = *t*-BuMe$_2$Si
14b, R = *i*-Pr$_3$Si
15

The catalytic enantioselective [4 + 2] cyclization of the siloxydiene-α,*β*-unsaturated esters **13a** and **13b** to **14a** and **14b**, respectively, was also investigated. The transformation **13a** → **14a** occurred cleanly with 0.2 equiv of **1** in CH_2Cl_2 (0.3 M) at −50 °C for 2 days and −20 °C for 1 day to give **14a** in 93% yield, 99% de and 96% ee.[17] The conversion of **13b** to **14b** was effected in 92% yield, 6:1 dr and 92% ee with 0.2 equiv of **1** in CH_2Cl_2 at 0 °C for 2 days.[17] Products **14a** and **14b** were converted to the same keto ester **15**, $[\alpha]^{27}_D$ +40 (c = 1.1, $CHCl_3$) by exposure to a solution of aqueous HCl−THF. Treatment of **15** with DBU in C_6H_6 at 80 °C for 2 h resulted in complete conversion to the 6/5 cis-fused hydrindanone. The absolute configuration of **15** was established by transformation into (+)-(octahydro-1-inden-4-yl)-methanol, $[\alpha]^{27}_D$ +30 (c = 0.6, $CHCl_3$), using the sequence (1) ethylenethioketal formation (ethanedithiol−BF_3·Et_2O, CH_2Cl_2), (2) reduction of COOMe to CH_2OH with $LiAlH_4$ in ether at 23 °C for 2 h, and (3) Raney nickel desulfurization in EtOH at reflux for 8 h. An authentic sample of (+)-(octahydro-1-inden-4-yl)methanol was synthesized from **5** by catalytic hydrogenation and carboxyl → CH_2OH reduction by $LiAlH_4$. An advantage of using **13b** over **13a** derives from the greater stability of the former which allows the reaction to be conducted at 0 °C.

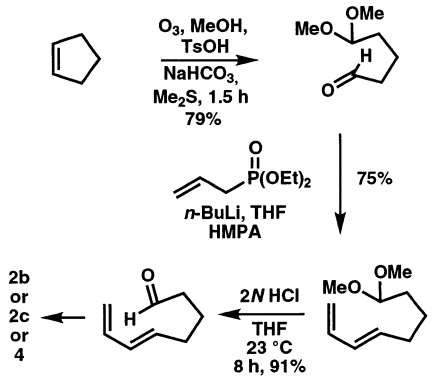


16 **17** **18**

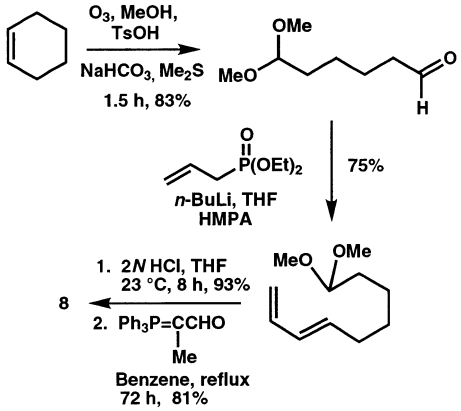
The construction of the decalin system from silyloxy-diene−α,*β*-unsaturated ester **16**, homologous reaction to **13** → **14**, was also investigated. As expected from the relative rates of cyclization of substrates **4** and **6**, as discussed above, the transformation **16** → **17** was considerably slower than **13** → **14**. Reaction of **16** catalyzed by 0.2 equiv of **1** at 40 °C, neat, for 12 h produced **17** as major product (90% ee) in 4:1 excess over the minor diastereomeric byproduct (corresponding *cis*-fused structure).[18] Treatment of **17** with THF-aqueous HCl produced the trans decalone **18**, $[\alpha]^{27}_D$ +26 (c = 1.1, $CHCl_3$).

The nine substrates for the intramolecular Diels−Alder reactions described above were synthesized readily using well-known methodology. Specifically, aldehydes **2b** and **2c** were made from the corresponding ethyl esters by reduction COOEt → CH_2OH (DIBAL-H) followed by Swern oxidation. The requisite esters were prepared by two-carbon Wittig coupling from *E*-5,7-octadienal that was made by the sequence shown in Scheme 1. Substrate **4** was also prepared from *E*-5,7-octadienal by Wittig condensation. Substrate **6** was similarly made from *E*-6,8-nonadienal whose synthesis and the further transformation to **8** are outlined in Scheme 2. In our experience, the synthetic pathways summarized in Schemes 1 and 2 are simpler and more effective than the previously described routes to such Diels−Alder substrates. The synthesis of **10** is summarized in Scheme 3.

Scheme 1



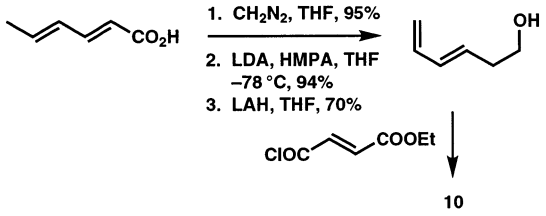
Scheme 2



The synthesis of the silyloxydienes **13a** and **13b** was accomplished by the sequence shown in Scheme 4. Substrate

(17) The relative stereochemistry of products **14a** and **14b** was determined from analysis of ^{1}H NMR/NOE data. The exo/endo ratio and enantioselectivity were determined by GC analysis of the desilylation product **15** using a J&W Scientific Cyclosil-B column (30 m × 0.25 mm, 150 °C, 25 psi), retention times: 16.29 min (exo), 16.88 min (exo), 17.71 min (endo, major), 18.63 min (endo, minor). The absolute configuration was determined by chemical correlation, as described.

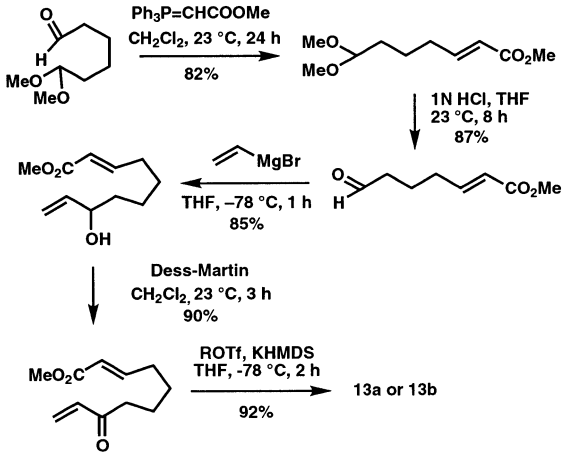
Scheme 3



16 was synthesized in an analogous manner from 7,7-dimethoxyheptanal (from ozonization of cycloheptene).

The experiments described above support the proposition that the oxazaborolidine **1** is a useful reagent for the Diels–Alder bicyclization of a variety of achiral triene substrates to form chiral bicyclo[4.3.0]nonane or bicyclo[4.4.0]decane derivatives with good yields and high enantioselectivities. Since the chiral ligand from which **1** is prepared, diphenylprolinol, is easily and efficiently recovered for reuse in each of the nine cases reported herein, this methodology is attractive for multistep synthesis. Another important feature is the predictability of absolute configuration of the internal Diels–Alder products. In each case described above, the mechanistic model accurately predicts the stereochemical course of the bicyclization reaction. The operational details of catalyst preparation and application to the bicyclization process are given in the illustrative procedures below.[19,20]

Scheme 4



Acknowledgment. This research was assisted financially by funding from Pfizer, Inc. We are grateful to Dr. Do Hyun Ryu for helpful advice and Dr. Richard Staples for the X-ray determination of structure **12**.

Supporting Information Available: Experimental data are given for the preparation of substrates and for the internal [4 + 2] cycloaddition reactions that are described herein. X-ray data for **12** are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The exo/endo ratio and the enantioselectivity were determined by GC analysis using a J&W Scientific Cyclosil-B column (30 m × 0.25 mm, 135 °C, 25 psi), retention times: 36.33 min (exo), 37.26 min (exo), 41.28 min (endo, major), 41.70 min (endo, minor). The absolute configuration was assigned from the dextrorotation of **18** and also by analogy with dextrorotatory ketone **15**.

(19) **Preparation of Catalyst 1.** A 100-mL, two-necked, round-bottomed flask equipped with a stir bar, a glass stopper, and a 50-mL pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 4 Å molecular sieves, and functioning as a Soxhlet extractor) fitted on top with a reflux condenser and a nitrogen inlet adapter was charged with (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol (41 mg, 0.16 mmol), tri-*o*-tolylboroxine (19 mg, 0.054 mmol), and 30 mL of toluene. The resulting solution was heated to reflux (bath temperature ~ 145 °C). After 4 h, the reaction mixture was cooled to ca. 60 °C and the addition funnel and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated by distillation (air-cooling) to a volume of ca. 10 mL. This distillation protocol was repeated three times by re-charging with 3 × 10 mL of toluene. The solution was then allowed to cool to room temperature and the distillation head was quickly replaced with a nitrogen inlet adapter. Concentration at (ca. 0.1 Torr for 30 min afforded the corresponding oxazaborolidine as a clear oil. To the neat waxlike oxazaborolidine precursor (0.16 mmol, theoretical) at −78 °C was added dropwise a solution of trifluoromethanesulfonimide (0.200 M in CH_2Cl_2, freshly prepared, 667 μL, 0.133 mmol). After 10−15 min at −20 °C, a colorless homogeneous solution of cationic catalyst **1** was obtained.

(20) **Synthesis of (+)-(4*R*,3a*R*,7a*R*)-4-Methyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carboxaldehyde (3b).** To a CH_2Cl_2 solution of 0.2 equiv of the freshly prepared catalyst **1** was added neat enal **2b** (109 mg, 0.665 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 108 h and then quenched by addition of 100 μL of Et_3N. After the mixture had warmed to room temperature, the residue was purified directly by silica gel chromatography (elution with hexane then hexanes−ether 20:1) to afford the Diels–Alder adduct **6** (101 mg, 93%) as a colorless oil: $[\alpha]^{20}_D = +10$ ($c = 1.06$, $CHCl_3$, 98% de, 90% ee); TLC (hexanes−EtOAc, 4:1), $R_f = 0.30$; ^{1}H NMR (500 MHz, $CDCl_3$) 9.48 (s, 1H, CHO), 5.84 (d, $J = 10.3$ Hz, 1H, H7), 5.59 (dq, $J = 2.6$, 10.2 Hz, 1H, H6), 2.44 (dq, $J = 3.4$, 18.1 Hz, 1H), 1.90 (m, 2H), 1.78 (dq, $J = 2.0$, 18.0 Hz, 1H), 1.70 (m, 2H), 1.54(m, 2H), 1.18 (m, 2H), 1.01 (s, 3H, Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 129.5, 124.5, 47.9, 46.6, 39.4, 33.6, 28.9, 23.8, 22.3, 12.6; MS *m*/*e* 164.0 (M^+); FTIR (film) 3019, 2957, 2870, 1725, 1684, 1456, 1397, 1267 cm^{-1}.