A New Chiral Rh(II) Catalyst for Enantioselective [2 + 1]-Cycloaddition. Mechanistic Implications and Applications

Yan Lou, Manabu Horikawa, Robin A. Kloster, Natalie A. Hawryluk, and E. J. Corey*

*Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138*

Received May 19, 2004; E-mail: corey@chemistry.harvard.edu

The use of rhodium(II) compounds (e.g., $Rh_2(OAc)_4$) as catalysts for the reactions of diazo compounds has developed into a major tool for chemical synthesis, especially for the cyclopropanation of olefins and the formation of rings by intramolecular C−H insertion.[1] Additionally, the ability of Rh(II) compounds to catalyze C−H insertion of sulfonyl, phosphoryl, and N-acyl iodosoimines has allowed oxidative cyclization with C−N bond formation to be effected in an analogous way.[2] Of great current interest are enantioselective versions of the Rh(II)-catalyzed diazocarbonyl cyclopropanation and C−H insertion reactions. The most effective of these chiral catalysts thus far have been Rh_2-bridged dimers having four identical chiral bridging ligands, especially the ligands of McKervey/Davies (N-arylsulfonylproline),[1i,3] Doyle (chiral 2-oxopyrrolidines),[1a,b,4] and Hashimoto/Ikegami (N-phthaloyl-*tert*-butylglycine).[1e,5] Despite extensive studies of the mechanism of these important Rh(II)-catalyzed processes and the achievement of very good enantioselectivities in numerous reactions, there is still no satisfactory understanding of the product-forming step of the cyclopropanation and C−H insertion processes or of the basis for enantioselection. It is clear that the rate-limiting step in the catalytic cycle is the nucleophilic attack of the α-diazocarbonyl substrate on the catalyst Rh_2X_4 to form a rhodium carbenoid complex after loss of nitrogen.[6,7] Although the structures of the intermediate reactive rhodium carbenoids have not been determined experimentally, they have generally been considered to retain the tetrabridged framework characteristic of $Rh_2(OAc)_4$.[8] The subsequent product-forming step has recently been studied computationally by two groups, each of which has assumed the involvement of the generally accepted tetrabridged rhodium carbenoid.[9,10]

In this paper we describe new developments concerning enantioselective [2 + 1]-cycloaddition reactions of ethyl diazoacetate, including the following: (1) invention of a novel chiral catalyst (**1**) that leads to the highly enantioselective and efficient conversion of acetylenes and olefins to cyclopropenes and cyclopropanes, respectively; (2) mechanistic insight that stimulated the design and discovery of the catalyst and that provides a clear and simple explanation of the product-determining events and the absolute stereochemical course of the reactions; and (3) a number of useful applications.
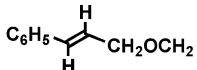
Catalyst **1** was synthesized from (R,R)-1,2-diphenylethylenediamine[11] by the following sequence: (1) carbonylation to the corresponding cyclic urea by reaction with (*tert*-BuCO)₂O and 4-(dimethylamino)pyridine in CH_3CN at 23 °C for 16 h (87% yield); (2) conversion to the mono-N-triflyl derivative (diphenyltriflylimidazolidinone, DPTI) by reaction with triflic anhydride and triethylamine in CH_2Cl_2 at −78 °C for ca. 1 h (92%); and (3) heating of DPTI thus obtained with $Rh_2(OAc)_4$ at reflux in chlorobenzene as a solvent using a Dean−Stark apparatus for removal of HOAc for ca. 20 h (71%).[12] The structure of the catalyst was determined by single-crystal X-ray diffraction analysis.[13] The remaining bridging acetate of $Rh_2(OAc)(DPTI)_3$ (**1**) is displaced much more slowly

than the other acetate ligands of $Rh_2(OAc)_4$, which accounts for the successful and efficient formation of **1**. Nonetheless, prolonged heating of **1** with >1 equiv of DPTI ligand in concentrated chlorobenzene solution at reflux with CaH_2−Celite 545 in a Soxhlet extractor for removal of HOAc produces $Rh_2(DPTI)_4$, the structure of which was determined to be **2** by single-crystal X-ray diffraction analysis.[13] Comparative experiments with **1** and **2** as catalysts (0.5 mol %) for the reaction of ethyl diazoacetate with olefins demonstrated that catalyst **1** is superior to **2** with regard to catalytic efficiency and enantioselectivity. Catalyst **1** is not only easier to prepare than **2** but also more robust and more readily recovered from catalytic reactions, an important ancillary factor because of the expense of rhodium. The focus on catalyst **1** was also mechanistically guided, as will be clear from the discussion below.


1   **2**
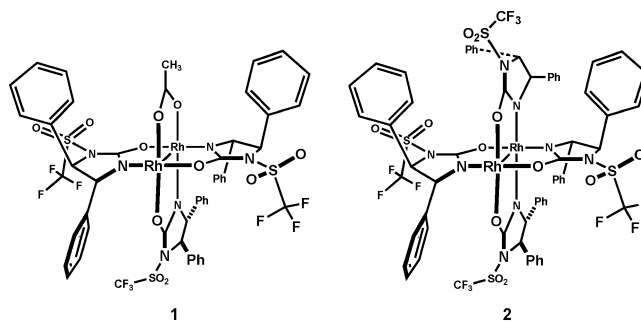
The addition of ethyl diazoacetate to a series of terminal acetylenes using 0.5 mol % **1** as a catalyst was selected for study for a number of reasons, including the following: (1) the only stereochemical issue is enantioselectivity, in contrast to olefinic substrates, which can give cis and trans [2 + 1]-cycloadducts; (2) ethyl diazoacetate, one of the most readily available, inexpensive, and useful diazo compounds, generally leads to poor enantioselectivity with the McKervey and Hashimoto catalysts; and (3) the cyclopropene products are more reactive and versatile synthetic intermediates than the cyclopropanes that result from terminal olefins (see below). The results of a study of the reaction of ethyl diazoacetate with a series of eight terminal acetylenes in the presence of 0.5 mol % **1** as a catalyst are summarized in Table 1. In each case, a 2-substituted-2-cyclopropene carboxylic acid ethyl ester was obtained with better average enantiomeric purity than previously reported.[14a] All products were dextrorotatory, indicating the same absolute configuration that was assigned from literature data.[14] In terms of enantioselectivity, yield, scope of reaction, and efficiency of catalyst recovery, catalyst **1** is outstanding.[14] Catalyst **1** also leads to considerably higher enantioselectivity than does catalyst **2** under the conditions of Table 1. For instance, the enantiomeric purity of the product of entry 2 of Table 1 is only 80% with catalyst **2** as compared with 93% for catalyst **1**. Entry 8 of Table 1 is of special interest because it shows that [2 +

Table 1. Catalyzed Enantioselective Addition of Ethyl Diazoacetate to Terminal Acetylenes


entry	R	yield, %	ee, %[a]
1	$CH_3(CH_2)_4$	90	95
2	$CH_3(CH_2)_5$	90	93
3	t-Bu	81	92
4	$(CH_3CH_2O)_2CH$	64	92
5	$BnOCH_2$	86	92
6	$MeOCH_2$	78	92
7	$BrCH_2$	62	95
8 [b]	C_6H_5 (alkene) CH_2OCH_2	76	95

[a] Enantiomeric purity for entries 1−7 was determined by GC analysis using either a Cyclosil B or γ-TA column; for entry 8, ee was determined by HPLC analysis using a Chiracel OJ column. Absolute configurations were assigned from comparison of rotation with literature values except for entries 2, 5, 7, and 8 for which the assignment followed from the observed dextrorotation. [b] Pentane was used as a solvent.

1]-cycloaddition of ethyl diazoacetate to the ene yne substrate occurs selectively at the acetylenic linkage.[15]
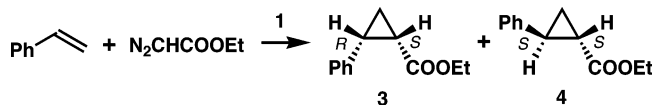

The reaction of ethyl diazoacetate and styrene with 0.5 mol % **1** as a catalyst (CH$_2$Cl$_2$, 23 °C) affords a 2:1 mixture of ethyl (1*S*,2*R*)-2-phenylcyclopropane carboxylate (**3**, 99% ee) and ethyl (1*S*,2*S*)-2-phenylcyclopropane carboxylate (**4**, 94% ee) in 84% yield. The formation of **3** and **4** implies high face-selectivity for the [2 + 1]-cycloaddition at the carbenoid center but only 2:1 π-facial selectivity at the olefinic linkage. Internal competition experiments with a mixture of 4-methoxystyrene and 4-nitrostyrene (N$_2$CHCOOEt, 0.5 mol % **1** in CH$_2$Cl$_2$ at 23 °C) demonstrated that the former olefin underwent reaction 1.7 times faster than the latter (97% ee for each of the two *cis*-cyclopropyl esters), a surprisingly small rate factor for a reaction thought to proceed by asynchronous attack of an electrophilic carbenoid on the terminal carbon of the double bond.[10] As expected, 1,1-diphenylethylene and ethyl diazoacetate (0.5 mol % **1**, CH$_2$Cl$_2$, 23 °C) gave the (*S*)-cyclopropyl ester **5** with high enantioselectivity (92% ee, 74% yield).
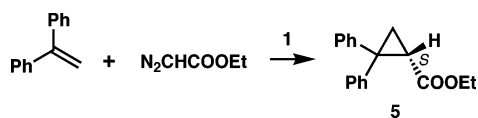
Catalyst **1** has also been found to be effective in promoting C−H bond insertion reactions, for example the conversion of **6** to **7** in 96% ee and 51% yield.[16]
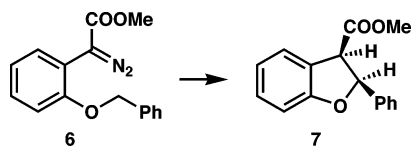

We advance a simple explanation for the enantioselectivity of the reactions catalyzed by **1**. We propose that the reactive form of the intermediate carbenoid derived from ethyl diazoacetate and **1** is the *tribridged* species **8** in which the *more labile acetate bridge* to the carbene-bearing rhodium has been broken. That cleavage allows the forward rhodium (now formally 1.5 valent) to form a much stronger dπ-bond to the carbene ligand that compensates for the acetate debridging. In **8** the carbene fragment, HCCOOEt, which in principle could attach to the Rh with COOEt either cis or trans to the Rh−O bond, is in the more favorable steric arrangement (COOEt s-cis to the Rh−O bond). We argue further that the product-forming step involves a [2 + 2]-cycloaddition of the 1-alkyne to **8**, as shown in **9**, followed by reductive elimination to form the (1*S*)-cyclopropene carboxylate, the observed major enantiomer, as shown in Table 1. It is important to note that the same enantiomeric cyclopropene would result if the roles of the two rhodiums in structures **8** and **9** are reversed, because of the C_2-symmetry of the two chelate rings orthogonal to the acetate bridge of **1**. An analogous mode of addition of styrene and 1,1-diphenylethylene to **8** leads to the observed products **3**−**5**. We believe that this type of pathway may be general for other Rh(II)-catalyzed cyclopropanations.[3−5,17]
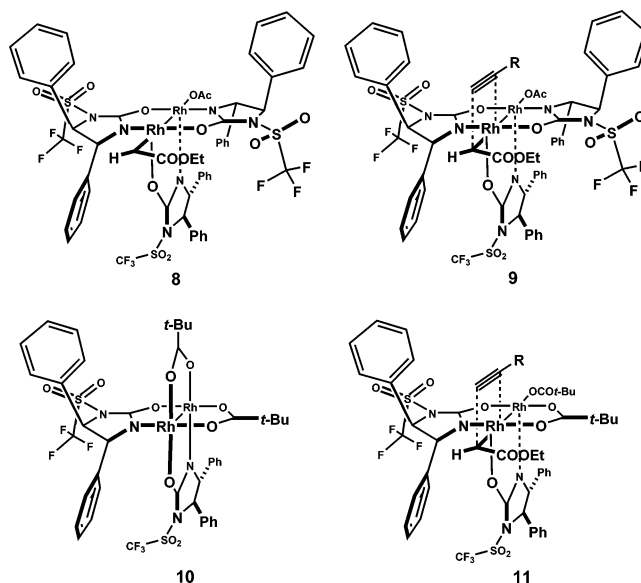

Powerful independent support for the mechanistic pathway described above has been obtained by the synthesis of complex **10** (structure proved by X-ray analysis), prepared from Rh$_2$(t-BuCO$_2$)$_4$ (chosen for its solubility) and (*R*,*R*)-DPTI, and the study of enantioselective [2 + 1]-cycloaddition of N$_2$CHCOOEt with a sampling of the terminal acetylenes of Table 1. For the cases corresponding to entries 2, 4, and 5, the same products were formed using **10** (0.05 mol %) instead of **1** with ee values of 91, 80, and 88%, respectively, under the conditions indicated in Table 1. The reaction of N$_2$CHCOOEt with styrene under catalysis by **10** (0.05 mol %) provided **3** (97% ee) and **4** (91% ee), nearly identical to the results with catalyst **1**. The similarity of results with catalysts **1** and **10** is readily explained in terms of transition states **9** and **11**. In contrast, there seems to be no way in which the good ee values obtained with **10** can be rationalized in terms of a *tetrabridged* carbenoid intermediate since the upper right quadrant of **10**, which is sterically most open for [2 + 1]-cycloaddition of acetylene to the carbenoid,[10] is also effectively achiral.

The chiral 2-substituted 2-cyclopropene-carboxylic esters that are available through the use of catalyst **1** in high enantiomeric

Scheme 1. Some Useful Transformations of Chiral Cyclopropenes
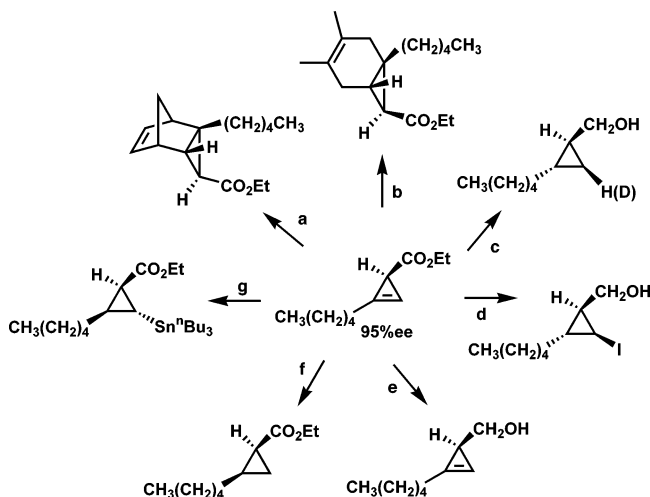
(a) Cyclopentadiene (10 equiv) in benzene at 23 °C for 12 h (94%). (b) 2,3-Dimethylbutadiene at 80 °C for 28 h (89%). (c) LAH (1.5 equiv) in Et₂O, then EtOAc, then H₂O or D₂O (80%). (d) LAH (2 equiv) in Et₂O, then EtOAC, then I₂ (71%). (e) DIBAL (2 equiv) in PhCH₃ for 1 h at −78 °C, then 1 h at 23 °C (83%). (f) 5% Pd on CaCO₃ (1 mol %) in EtOAc with H₂ (1 atm) 2 h (92%). (g) Pd(PPh₃)₄ (1 mol %) and n-Bu₃SnH (1.1 equiv) in THF at −78 °C for 1 h (82%).

Scheme 2. Synthesis of (9R,10S)-Dihydrosterculic Acid
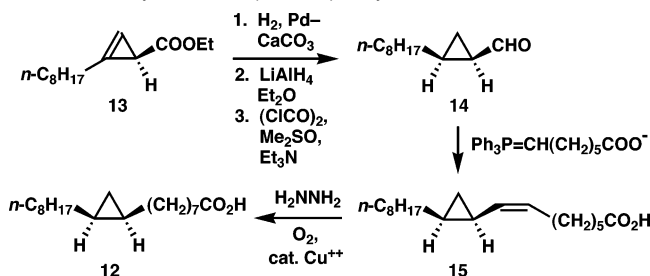
purity are valuable and versatile synthetic intermediates. Scheme 1 details a number of interconversions that have been carried out with ethyl (1S)-2-n-pentyl-2-cyclopropene-carboxylate.[18] It is noteworthy that the reductive transformations c and f of Scheme 1 afford access to the cis or trans cyclopropyl derivatives that would result from cyclopropanation of terminal olefins, but without problems of cis/trans stereoselectivity.

We have also applied the methodology described above to the first enantioselective synthesis of the naturally occurring fatty acid (9R,10S)-dihydrosterculic acid (**12**), a common cyclopropyl fatty acid of microorganisms and subtropical plants.[19] The chiral cyclopropene **13** (87% ee), which is readily available from ethyl diazoacetate and 1-decyne using the enantiomer of catalyst **1** (synthesized starting from (S,S)-diphenylethylenediamine), was converted to the cis aldehyde **14** by the sequence: (1) catalytic reduction using 5% Pd–CaCO₃ and 1 atm of H₂ in EtOAc at 23 °C for 2 h (90%); (2) reduction of COOEt to CH₂OH using LiAlH₄ in ether at 23 °C for 1 h (78%); and (3) Swern oxidation of CH₂OH to CHO with Me₂SO and oxalyl chloride in CH₂Cl₂ at −78 °C followed by Et₃N and warming to 23 °C (95%). Wittig coupling of aldehyde **14** with the ylide from 7-triphenylphosphonioheptanoic acid bromide and 2 equiv of LDA in THF at −78 to 23 °C produced the unsaturated acid **15** (72%, Z/E = 4:1), which was reduced by stirring with H₂NNH₂ and air in ethanol containing a catalytic amount of CuSO₄ (via diimide, N₂H₂) to afford (9R,10S)-dihydrosterculic acid as a colorless solid, mp 29–30 °C, in 85% yield. This synthesis is much shorter than a recently published process

for the synthesis of the structurally related fatty acid (11R,12S)-lactobacillic acid.[20]

Note Added after ASAP Posting. After this paper was posted ASAP on 06/30/2004, structures **8**−**11** were corrected and the reaction conditions were added to Scheme 1. The corrected version was posted 07/06/2004.

Supporting Information Available: Experimental procedures for reactions and X-ray structural data for **1**, **2**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley: New York, 1998. (b) Doyle, M. P.; Ren, T. In *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; John Wiley: New York, 2001; pp 113−168. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 2861−2908. (d) Forbes, D. C.; McMills, M. C. *Curr. Org. Chem.* **2001**, 5, 1091−1105. (e) Hashimoto, S. *Farumashia* **2001**, 37, 1095−1097. (f) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, 98, 911−935. (g) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, 54, 7919−7946. (h) Kitagaki, S.; Hashimoto, S. *Yuki Gosei Kagaku Kyokaishi* **2001**, 59, 1157−1168. (i) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, 617−618. (j) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459−2469.
(2) See: (a) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, 5, 4823−4826. (b) Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, 125, 2028−2029. (c) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, 40, 598−600. (d) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, 123, 6935−6936.
(3) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361−362.
(4) (a) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, 31, 6613−6616. (b) Doyle, M. P.; Zhou, Q. L.; Simonsen, S. H.; Lynch, V. *Synlett* **1996**, 697−698. (c) Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Müller, P.; Bernardinelli, G.; Ene, D.; Motallebi, S. *Helv. Chim. Acta* **1993**, 76, 2227−2235.
(5) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, 31, 5173−5174.
(6) (a) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, 116, 8991−9000. (b) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1996**, 118, 8162−8163. (c) Pirrung, M. C.; Liu, H.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2002**, 124, 1014−1023.
(7) Alonso, M. E.; García, M. del C. *Tetrahedron* **1989**, 45, 69−76.
(8) (a) Sheehan, S. M.; Padwa, A.; Snyder, J. P. *Tetrahedron Lett.* **1998**, 39, 949−952. (b) Snyder, J. P.; Padwa, A.; Stengel, T. *J. Am. Chem. Soc.* **2001**, 123, 11318−11319.
(9) (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, 124, 7181−7192. (b) Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2003**, 345, 1159−1171.
(10) Nowlan, D. T., III; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, 125, 15902−15911. These workers have also measured ¹²C/¹³C kinetic isotope effects for olefin cyclopropanation.
(11) Available from Aldrich Co. or as described in: Pikul, S.; Corey, E. J. *Org. Synth. Coll. Vol. IX* **1998**, 387−390.
(12) Reaction time was generally determined by TLC analysis of the reaction mixture (10:1 C₆H₆−CH₃CN) periodically. A mixture of anhydrous Na₂CO₃ and 4 Å molecular sieves was placed in the trap arm of the Dean−Stark apparatus to facilitate removal of HOAc from the distillate of C₆H₅Cl.
(13) For full details, see Supporting Information. NMR spectra were also in accord with the assigned structure.
(14) (a) Doyle, M.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. *J. Am. Chem. Soc.* **1994**, 116, 8492−8498. (b) Protopopova, M.; Doyle, M.; Müller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, 114, 2755−2757. (c) Müller, P.; Imogaï, H. *Tetrahedron: Asymmetry* **1998**, 9, 4419−4428.
(15) In this connection, we have determined that the reaction of ethyl diazoacetate and 0.5 mol % **1** in CH₂Cl₂ at 23 °C with 1-nonyne is 2.4 times as fast as with 1-nonene.
(16) Trans isomer of **7** was also formed as a minor product (ratio 5:1).
(17) These analyses will be detailed in a subsequent publication. Even if the intermediate Rh−carbene complex is an equilibrating mixture of tetra-bridged and tribridged species (the latter analogous to **8**) and even if the tribridged species is only a minor component of that equilibrium, the metallacyclobutane pathway (e.g., as in **9**) proposed herein could still dominate kinetically.
(18) For recent reviews of transformations on cyclopropenes, see: (a) Baird, M. S. Cyclopropanes: Synthesis: From Cyclopropenes. In *Houben-Weyl*; Thieme: Stuttgart, 1997; pp 114−255. (b) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, 103, 1295−1326.
(19) (a) Grogan, D. W.; Cronan, J. E., Jr. *Microbiol. Mol. Biol.* **1997**, 61, 429−441. (b) Stuart, L. J.; Buist, P. H. *Tetrahedron: Asymmetry* **2004**, 15, 401−403.
(20) Coxon, G. D.; Al-Dulayymi, J. R.; Baird, M. S.; Knobl, S.; Roberts, E.; Minnikin, D. E. *Tetrahedron: Asymmetry* **2003**, 14, 1211−1222.