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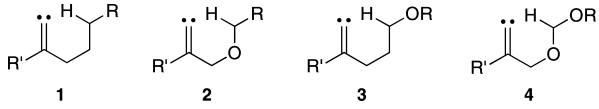
Stereoelectronic Effect for the Selectivity in C−H Insertion of Alkylidene Carbenes and Its Application to the Synthesis of Platensimycin

Sang Young Yun, Jun-Cheng Zheng, and Daesung Lee*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

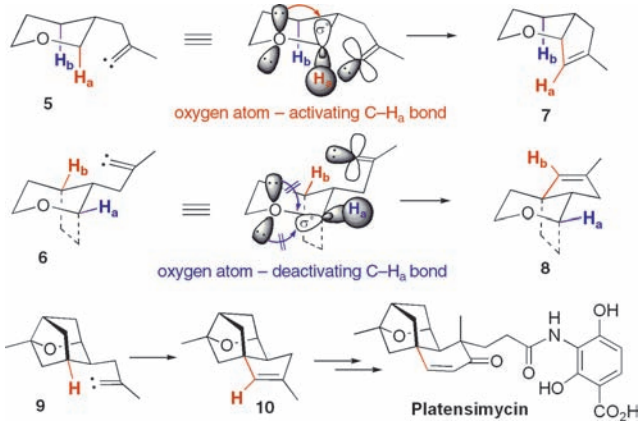
Received April 30, 2009; E-mail: dsunglee@uic.edu

The insertion of alkylidene carbenes into C−H bonds is a powerful synthetic tool for constructing stereochemically defined quaternary carbon centers.[1] Various forms of alkylidene carbene species, including **1**−**4**, have been studied for their reactivity and employed in natural product syntheses.[2] In general, the C−H bonds become more reactive toward carbene insertion if an oxygen atom is directly connected to the reacting C−H bond.[3] However, how the oxygen atom activates the C−H bonds toward insertion or how much it contributes to the reactivity of the C−H bonds in **2** and **3** relative to that in **1** has not been elucidated.



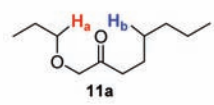
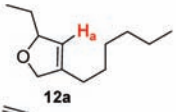
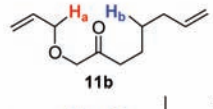
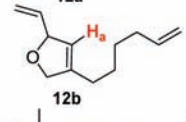
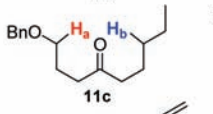
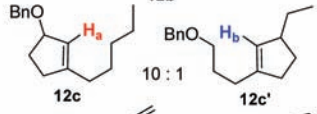
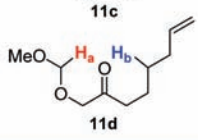
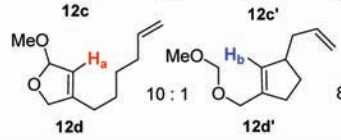
If the activating role of oxygen is due to its lone-pair electrons through n(O) → σ^*(C−H) electron delocalization, the extent of its (stereo)electronic effect would be very different among **2**−**4** in view of the cyclic nature of transition state for the C−H insertion.[3a,4] This hypothesis can be tested with substrates containing combinations of competing carbene moieties **1**−**4**. A comparison of the reactivities and selectivities of conformationally constrained systems **5** and **6** would be particularly instrumental. If the predicted stereoelectronic effect of the oxygen is important, carbene **5** would generate **7** via selective insertion into the axial (O)C−H_a bond. On the other hand, insertion of carbene **6** would take place at (C)C−H_b bond to generate **8** because in this case the oxygen just deactivates the (O)C−H_a bond inductively (Scheme 1). In this communication, we report a systematic study of C−H insertion reactions that reveals a strong stereoelectronic effect of oxygen. The utility and scope of the regioselective C−H insertion process was further demonstrated with carbene **9** to construct the ring-junction quaternary carbon center of **10**, providing rapid access to an immediate precursor for platensimycin.

Scheme 1. Selective C−H Insertion of Alkylidene Carbenes



First, the effect of the oxygen atom in C−H insertion was examined with substrates where the oxygen substituent becomes endocyclic (**11a**, **11b**), exocyclic (**11c**), or both (**11d**) in the incipient rings (Table 1). Insertion reactions of **11a** and **11b** occurred exclusively with the C−H_a bonds on the carbon carrying the oxygen atom, providing **12a** and **12b** in 90 and 74% yields, respectively. On the other hand, insertion with **11c** afforded a mixture of **12c** and **12c′** in a 10:1 ratio (96%), which might be due to a less pronounced effect of the exocyclic oxygen of the incipient ring compared with that of the corresponding endocyclic oxygen in **12b**. We anticipated that substrate **11d** with both endo- and exocyclic oxygen substituents should be doubly activating and thus would provide a larger ratio of **12d** over **12d′**. However, products **12d** and **12d′** were formed in a 10:1 ratio and 86% yield. This result implies that only one of the oxygens plays an activating role for the C−H insertion.

Table 1. Selective C−H Insertion of Alkylidene Carbenes[a]

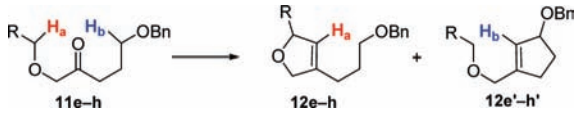
Entry	Substrates	Products	Yield
1			90%
2			74%
3			96%
4			86%

[a] Reaction conditions: $TMSCHN_2$ (1.5 equiv), *n*-BuLi (1.6 equiv), −78 °C to room temperature in THF over 3 h.

Next, we examined the insertion behavior of substrates **11e**−**h**, where the oxygen exo to the incipient ring remains constant (OBn) while the endo oxygen substituent varies (Table 2). Insertions with **11e** and **11f** afforded 2:1 and 1.5:1 ratios of **12e** to **12e′** (96%) and **12f** to **12f′** (89%), respectively. On the other hand, **11g** and **11h** showed the reverse preference for the insertion, providing 0.7:1 and 0.5:1 ratios of **12g** to **12g′** (82%) and **12h** to **12h′** (80%). Clearly, a general trend in the selectivity emerged from these reactions: the activating effect of the endocyclic oxygen is more pronounced than that of the exocyclic oxygen, but the extent of their effects depends on the nature of their substituents. The deactivating effect of the exo oxygen substituent (a methoxy group) in **11h** (as well as in **11d**) for C−H_a insertion was rather unexpected.

10.1021/ja903526g CCC: $40.75

Table 2. Selectivity in C−H Insertion of Alkylidene Carbenes[a]

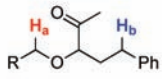
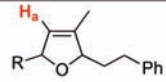
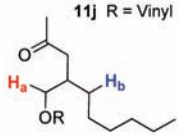
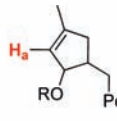
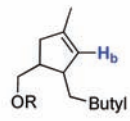


Entry		R	Yield (**12**+**12'**)	Ratio (**12** : **12'**)
1	**11e**		96%	2 : 1
2	**11f**		89%	1.5 : 1
3	**11g**		82%	0.7 : 1
4	**11h**		80%	0.5 : 1

[a] Reaction conditions were same as in Table 1.

Next, insertion reactions of substrates bearing a branching point at either the β- (**11i**, **11j**) or γ-position (**11k**, **11l**) relative to the carbenic carbon were examined (Table 3). Both substrates **11i** and **11j** afforded products **12i** (82%) and **12j** (85%) via selective insertion into the C−H_a bond of the carbon carrying the oxygen atom. On the other hand, substrates **11k** and **11l** having γ-branches with OBn and OTBS groups, respectively, on the carbon undergoing the C−H insertion generated 7:1 mixtures of **12k**/**12k′** and **12l**/**12l′** mixtures in 88 and 76% yields, respectively. The lack of the competing insertion into the relatively more reactive benzylic C−H_b on **11i**/**11j** as opposed to the participation of the less reactive C−H_b in **11k**/**11l** is noteworthy. This difference is another piece of evidence supporting the general trend that the oxygen endo to the incipient ring activates the C−H bond more effectively for C−H insertion than the corresponding exo oxygen substituent.

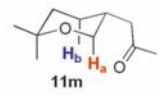
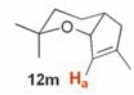
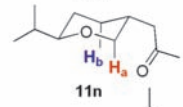
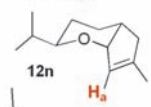
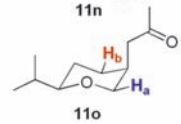
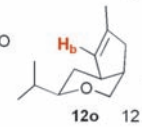
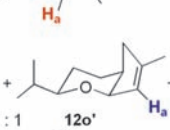
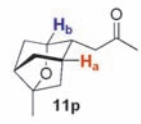
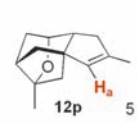
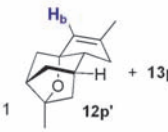
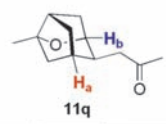
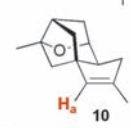
Table 3. Selectivity in C−H Insertion of Branched Carbenes[a]

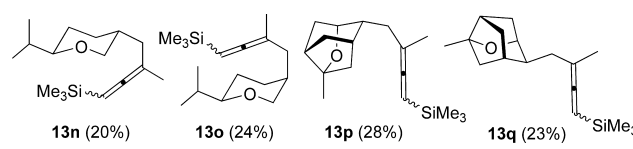
Entry	Substrates	Products			Yield
1	 **11i** R = Ethyl	 **12i**			82%
2	**11j** R = Vinyl	**12j**			85%
3	 **11k** R = Bn	 **12k**	7 : 1	 **12k'**	88%
4	**11l** R = TBS	**12l**	7 : 1	**12l'**	76%

[a] Reaction conditions were the same as in Table 1.

To gain further insight into the factors that affect the regioselectivity of the insertion, pyran-containing substrates **11m**−**q** were examined (Table 4). As expected, the selective insertion into the C−H_a bonds of the pyran rings of **11m** and **11n** provided products **12m** and **12n** in 69 and 65% yield, respectively. Allene **13n** was also formed in 20% yield from **11n** as a result of a competing intermolecular reaction of the alkylidene carbene intermediate with trimethylsilyl diazomethane, which is probably due to a reduced rate of C−H insertion in this cyclic system.[5] The cis-1,4-disubstituted substrate **11o**, on the other hand, provided predominantly **12o** via insertion into the seemingly less reactive C−H_b bond and the minor product **12o′** in a 12:1 ratio (62%) together with 24% of allene **13o**. We believe that the opposite C−H insertion regioselectivities of **11n** and **11o** are caused by the stereoelectronic effect depicted in Scheme 1. Similarly, reaction of substrates **11p** and **11q** afforded products **12p** and **10** via preferred insertion into the C−H_a bonds attached to the carbon not carrying the oxygen atom,

Table 4. Selectivity in Conformationally Constrained Pyrans

Entry	Substrates	Products			Yield (**12**/**10**)
1	 **11m**	 **12m**			69%
2	 **11n**	 **12n**	+ **13n**		65%
3	 **11o**	 **12o**	12 : 1	 **12o'** + **13o**	62%
4	 **11p**	 **12p**	5 : 1	 **12p'** + **13p**	35%
5	 **11q**	 **10**	+ **13q**		65%

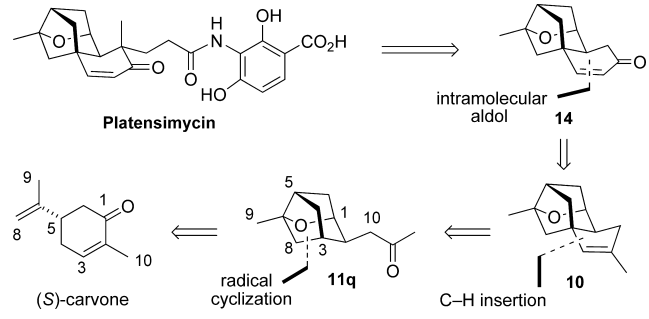


which further supports the strong stereoelectronic and inductive effects of oxygen with respect to the reactivity of the C−H bond.

With the regioselective formation of **10**, we embarked on the synthesis of platensimycin, a potent antibacterial agent against gram-positive bacteria including the multi-drug-resistant strains of staphylococci and enterococci.[6] Because of its novel mechanism of action and structural features, platensimycin has drawn significant interest from both the synthetic and medical communities.[7] Since Nicolaou's first total synthesis, many elegant syntheses of platensimycin and its analogues have been reported.[8,9] The current strategy harnessing the C−H insertion to form one of the key quaternary carbon centers of the platensimycin core would constitute a unique synthetic approach.

From a retrosynthetic perspective, platensimycin would be derived from tetracyclic core **14** through established methods (Scheme 2). Enone **14** could be realized via an oxidative double bond cleavage of **10** followed by an intramolecular aldol reaction. The cyclopentene motif of **10** in turn would be installed by the regioselective C−H insertion of alkylidene carbene generated from **11q** by adding lithiated trimethylsilyl diazomethane.[1,10] The five-membered carbocycle in **11q** would be constructed on the inter-

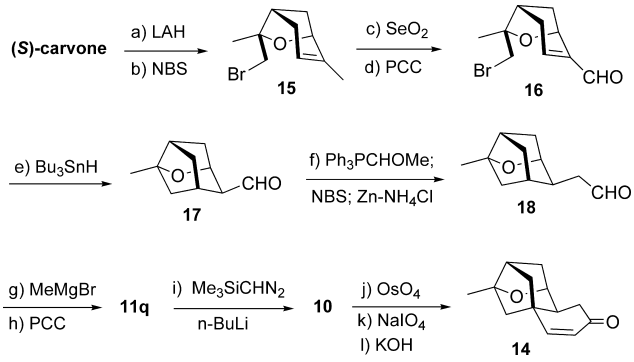
Scheme 2. Retrosynthetic Analysis of Platensimycin



mediate derived from (*S*)-carvone via radical-mediated C−C bond formation between C8 and C3.

Our synthetic sequence (Scheme 3) commenced with the stereoselective reduction of commercially available (*S*)-carvone with LAH (−78 °C, 15:1 selectivity) followed by bromoetherification of the crude alcohol (NBS, −78 °C), generating bridged oxabicycle **15** (12:1 selectivity).[11] The stereochemistry at the newly formed quaternary center was inferred on the basis of similar transformations[8g,12] and ultimately confirmed in the following stage.[13] Allylic oxidation of **15** yielded a mixture of aldehyde **16** and the corresponding allylic alcohol, which was further oxidized to **16** with PCC. Radical-mediated cyclization of **16**[14] was proved to depend critically on the reaction temperature. An initial attempt at 100 °C gave **17** as a mixture of epimers in a 2.5:1 ratio with 75% yield, while lowering the reaction temperature to ∼65 °C improved both the yield and selectivity (81%, 4.5:1). To elaborate aldehyde **17** to form the tetracyclic enone core of platensimycin, a one-carbon homologation was performed in a two-step sequence involving a

Scheme 3. Synthesis of the Tricyclic Caged Framework[a]



[a] (a) LAH, Et_2O, −78 °C. (b) NBS, THF, −78 °C, 86% over two steps. (c) SeO_2, AcOH/CH_2Cl_2. (d) PCC, CH_2Cl_2, 61% over two steps. (e) AIBN (0.1 equiv), Bu_3SnH, benzene, 65 °C, 81%. (f) Ph_3PCH_2OMeCl, *n*-BuLi, THF, −78 °C to rt; NBS, THF/H_2O (10:1), 0 °C to rt; NH_4Cl(aq), Zn. (g) MeMgBr, THF, 0 °C, 66% over two steps. (h) PCC, CH_2Cl_2, 98%. (i) Me_3SiCHN_2, *n*-BuLi, THF, −78 °C to rt. (j) OsO_4, NMO, pyridine (2 equiv), acetone/H_2O (4:1), 40 °C, 48 h, 45% over two steps. (k) $NaIO_4$ (2 equiv), THF/H_2O (1:1). (l) KOH (5 equiv), EtOH, 86% over two steps.

Wittig reaction followed by treatment with NBS/zinc powder,[9d] delivering aldehyde **18**. Subsequent addition of methyl Grignard reagent gave the corresponding alcohol, which was oxidized to ketone **11q** in quantitative yield. The treatment of ketone **11q** with lithiated trimethylsilyl diazomethane afforded C−H insertion product **10** and allene byproduct **13q** in a 3:1 ratio. Dihydroxylation of **10** followed by oxidative cleavage of the resulting diol with $NaIO_4$ afforded a ketoaldehyde intermediate, treatment of which with KOH provided enone **14** in excellent yield. The ^1H and ^{13}C NMR spectra of **14** were identical to those reported by Nicolaou and others.[8]

In summary, a systematic study of C−H insertion reactions with variously substituted and conformationally constrained substrates was carried out. High selectivity in the insertion between two competing C−H bonds was observed and is believed to be the manifestation of a strong stereoelectronic effect of oxygen substituents. This regioselective C−H insertion reaction was employed as a platform to develop a concise asymmetric synthesis of platensimycin. The tetracyclic core of platensimycin was obtained starting from commercially available (*S*)-carvone in 11 steps with 8% overall yield without the need to manipulate protecting groups. Further study to elucidate the origin of the selectivity in C−H insertions is in progress.

Acknowledgment. We thank UIC for financial support and Dr. Don Wink for the X-ray structure determination of **16**.

Supporting Information Available: Complete refs 6a, 6b, and 8p; general procedures; crystallographic data for **16** (CIF); and characterization data for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (b) Taber, D. F. In *Methods of Organic Chemistry*, 4th ed.; Helmchen, G., Ed.; Georg Thieme Verlag: New York, 1995; Vol. E21, p 1127. (c) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164. (d) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795.

(2) (a) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656. (b) Taber, D. F.; Walter, R.; Meagley, R. P. *J. Org. Chem.* **1994**, *59*, 6014. (c) Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723. (d) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416. (e) Wardrop, D. J.; Zhang, W.; Fritz, J. *Org. Lett.* **2002**, *4*, 489. (f) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768. (g) Taber, D. F.; Sikkander, M. I.; Storck, P. H. *J. Org. Chem.* **2007**, *72*, 4098.

(3) (a) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557. (b) Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749. (c) Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997**, *38*, 4927. (d) Davis, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *J. Org. Chem.* **2003**, *68*, 6126. For recent reviews on C−H functionalization, see: (e) Davis, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (f) Davis, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, *3*, 4176.

(4) (a) Dobson, R. C.; Hayes, D. M.; Hoffmann, R. *J. Am. Chem. Soc.* **1971**, *93*, 6188. (b) Bodor, N.; Dewar, M. J. S.; Wasson, J. S. *J. Am. Chem. Soc.* **1972**, *94*, 9095. (c) Jug, K.; Mishra, P. C. *Int. J. Quantum Chem.* **1983**, *23*, 887.

(5) Further studies of the formation of allenes will be reported elsewhere.

(6) (a) Wang, J.; et al. *Nature* **2006**, *441*, 358. (b) Singh, S. B.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 11916.

(7) For biosynthesis, see: (a) Herath, K. B.; Attygalle, A. B.; Singh, S. B. *J. Am. Chem. Soc.* **2007**, *129*, 15422. (b) Herath, K.; Attygalle, A. B.; Singh, S. B. *Tetrahedron Lett.* **2008**, *49*, 5755.

(8) (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086. (b) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942. (c) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825. (d) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922. (e) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8074. (f) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534. (g) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921. (h) Nicolaou, K. C.; Pappo, D.; Tsang, K. Y.; Gibe, R.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 944. (i) Kim, C. H.; Jang, K. P.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4009. (j) Matsuo, J.-I.; Takeuchi, K.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 4049. (k) Ghosh, A. K.; Xi, K. *J. Org. Chem.* **2009**, *74*, 1163. For reviews, see: (l) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2548. (m) Nicolaou, K. C.; Chen, J. S.; Edmonds, D. J.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 660. For syntheses of analogues, see: (n) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Montero, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4712. (o) Nicolaou, K. C.; Tang, Y.; Wang, J.; Stepan, A. F.; Li, A.; Montero, A. *J. Am. Chem. Soc.* **2007**, *129*, 14850. (p) Nicolaou, K. C.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 13110. (q) Yeung, Y.-Y.; Corey, E. J. *Org. Lett.* **2008**, *10*, 3877.

(9) For syntheses of platencin, see: (a) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1780. (b) Hayashida, J.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4373. (c) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6199. (d) Yun, S. Y.; Zheng, J.-C.; Lee, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 6201. (e) Waalboer, D. C. J.; Schaapman, M. C.; van Delft, F. L.; Rutjes, F. P. J. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6576. (f) Nicolaou, K. C.; Toh, Q.-Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 11292. (g) Austin, K. A. B.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2008**, *10*, 4465. (h) Tiefenbacher, K.; Mulzer, J. *J. Org. Chem.* **2009**, *74*, 2937. (i) Varseev, G. N.; Maier, M. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3685.

(10) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151.

(11) Bellesia, F.; Grandi, R.; Pagnoni, U. M.; Trave, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 851.

(12) (a) Corey, E. J.; Pearce, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 5841. (b) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131.

(13) The X-ray diffraction analysis of compound **16** was carried out with (*R*)-carvone-derived compound.

(14) Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883.

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