Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 715–719

TETRAHEDRON LETTERS

A new strategy in enantioselective intramolecular hetero Diels–Alder reaction: catalytic double asymmetric induction during the tandem transetherification–intramolecular hetero Diels–Alder reaction of methyl (*E*)-4-methoxy-2-oxo-3-butenoate with *rac*-6-methyl-5-hepten-2-ol

Hidetaka Koga[a] and Eiji Wada[b,*]

[a]*Department of Molecular and Material Science, Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan*

[b]*Institute of Advanced Material Study, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan*

Received 28 October 2002; revised 20 November 2002; accepted 22 November 2002

Abstract—An efficient catalytic double asymmetric induction during the tandem transetherification–intramolecular hetero Diels–Alder reaction has been developed. The enantioselective tandem reaction of methyl (*E*)-4-methoxy-2-oxo-3-butenoate with *rac*-6-methyl-5-hepten-2-ol has been achieved to provide methyl (2*R*,4a*S*,8a*R*)-3,4,4a,8a-tetrahydro-2,5,5-trimethyl-2*H*,5*H*-pyrano[4,3-*b*]-pyran-7-carboxylate in good yield with effective kinetic resolution (up to 95% selectivity), high diastereoselectivity (up to 92% de), and high enantioselectivity (up to 97% ee) in the presence of (*S*,*S*)-*tert*-Bu-bis(oxazoline)-Cu(SbF_6)$_2$ and 5 Å molecular sieves.

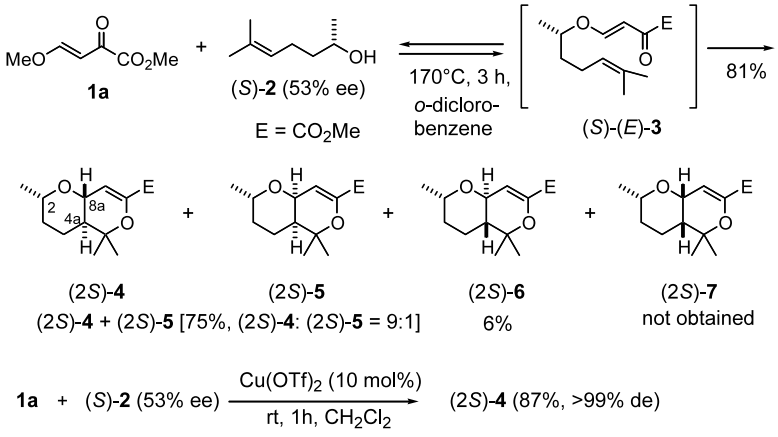
Impressive progress has recently been made in catalytic asymmetric reactions which attain the synthesis of various optically active compounds with high optical purity. The development of a new type of catalytic asymmetric induction is a challenging target in organic synthesis.[1] However, the development of a catalytic asymmetric induction of intramolecular hetero Diels–Alder reaction with α,β-unsaturated carbonyl compounds as hetero 1,3-dienes, which is a convenient method for the construction of optically active polyheterocyclic skeleton, still remains as a relatively unexplored field.[2] On the other hand, the tandem reaction is a most powerful methodology in organic synthesis to form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents. Therefore, the development of a variety of tandem reactions has been undertaken.[3]

Recently, we described a new type of catalytic single asymmetric induction of tandem transetherification–intramolecular hetero Diels–Alder reaction of methyl (*E*)-4-methoxy-2-oxo-3-butenoate (**1a**) with *prim*- and *tert*-δ,ε-unsaturated alcohols leading to hydropyranopyrans with absolute stereoselectivity and excellent enantioselectivity (up to 98% ee) by using (*S*,*S*)-*tert*-Bu-bis(oxazoline)-Cu(SbF_6)$_2$ **A** as catalyst in the presence of 5 Å molecular sieves (MS).[4,5]

As part of our efforts to expand the scope of asymmetric induction of this tandem reaction, we report here the preliminary studies on double asymmetric induction[6] of enone **1** with *racemic sec*-δ,ε-unsaturated alcohol *rac*-**2** in the presence of chiral Lewis acid catalyst **A** and 5 Å MS. In the first step, the tandem reaction of enone **1a** with the (*S*)-enriched enantiomer of 6-methyl-5-hepten-2-ol (*S*)-**2** (53% ee), which was prepared by catalytic asymmetric reduction of 6-methy-5-hepten-2-one according to the procedure of Itoh,[7] was allowed to react under thermal and a Lewis acid catalyst conditions to confirm the absolute configuration of cycloadducts (Scheme 1). The reaction of enone **1a** (1.5 equiv.) with alcohol (*S*)-**2** was performed in *o*-dichlorobenzene for 3 h at 170°C, then carefully subjected to silica gel column chromatography. Theoretically, four diastereomeric cycloadducts (2*S*)-**4**–**7** can be formed by this reaction. However, three

Keywords: double asymmetric induction; intramolecular hetero Diels–Alder reaction; chiral Lewis acid; enantioselective reactions; tandem reaction; 1-oxa-1,3-butadiene; transetherification; molecular sieves.
* Corresponding author. Tel.: + 81-92-583-7803; fax: + 81-92-583-7803; e-mail: wada@cm.kyushu-u.ac.jp

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02706-5

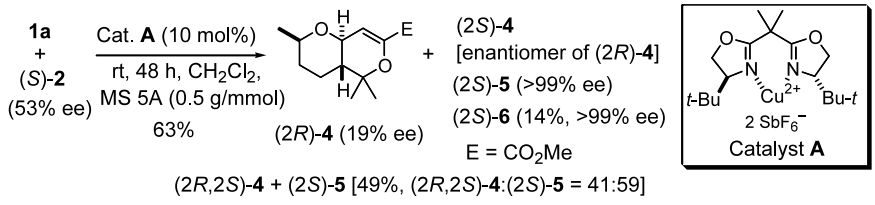


Scheme 1.

diastereomeric cycloadducts were obtained as a mixture of (2*S*)-**4** (4a,8a-*trans*) and (2*S*)-**5** (4a,8a-*cis*) [(2*S*)-**4**:(2*S*)-**5** = 90:10] in 75% yield, in addition to (2*S*)-**6** (4a,8a-*trans*) in 6% yield with retention of enantiomeric excess of alcohol (*S*)-**2**, respectively. On the other hand, the reaction with $Cu(OTf)_2$ (10 mol%) for 1 h at room temperature afforded a single diastereomeric cycloadduct (2*S*)-**4** (>99% de) in 87% yield with retention of enantiomeric excess of alcohol (*S*)-**2**. The stereochemistry of the above hydropyranopyrans (2*S*)-**4**–**6** was determined on the basis of ^{1}H NMR spectral data. The stereoisomer (2*S*)-**4** was confirmed to be the 2,8a-*cis*-8a,4a-*trans* structure based on the large vicinal couplings for J_{8a-4a} (10.0 Hz) as well as the notable NOEs between H-2/H-8a. Similar structural analysis by ^{1}H NMR spectral data was applied to (2*S*)-**5** (J_{8a-4a} = 6.1 Hz and notable NOEs between both H-8a/H-4a and H-8/H-2ax) and (2*S*)-**6** (J_{8a-4a} = 10.1 Hz and notable NOEs between both 2-Me/H-8a and H-2/H-4a). Thus, each stereoisomer (2*S*)-**5** and (2*S*)-**6** has been determined to be 2,8a-*trans*-8a,4a-*cis* and 2,8a-*trans*-8a,4a-*trans* structure, respectively.[8] The absolute configuration of (2*S*)-**4**, (2*S*)-**5**, and (2*S*)-**6** was defined as 2*S*,4a*S*,8a*S*, 2*S*,4a*S*,8a*R*, and 2*S*,4a*R*,8a*R*, respectively, based on the relative stereochemistry mentioned above.

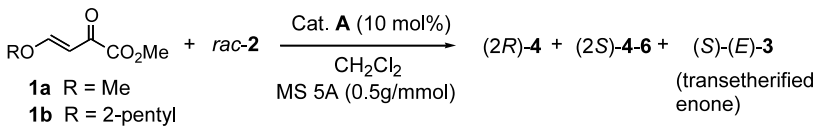
Next, chiral Lewis acid-promoted reaction was investigated to find the matching pair of chirality of alcohol (Scheme 2). When the reaction of enone **1a** with (*S*)-**2** (53% ee) was carried out in CH_2Cl_2 for 48 h at room temperature with (*S*,*S*)-*tert*-Bu-bis(oxazoline)-$Cu(S_bF_6)_2$ **A** (10 mol%) as catalyst in the presence of 5 Å MS (0.5 g/mmol), a mixture of cycloadducts (2*R*,2*S*)-**4** [(2*R*)-**4** (19% ee)] and (2*S*)-**5** (>99% ee) [(2*R*,2*S*)-**4**:(2*S*)-**5** = 41:59] was isolated in 49% yield; in addition, (2*S*)-**6** (>99% ee) was obtained in 14% yield. This result shows that the reaction with the matching pair of alcohol (*R*)-**2** gives only one cycloadduct (2*R*)-**4** and the mismatching pair of alcohol (*S*)-**2** gives three diastereomeric cycloadducts (2*S*)-**4**–**6**.

Thus, we undertook investigation of the double asymmetric induction of a tandem reaction of **1a** with *rac*-**2** in CH_2Cl_2 in the presence of catalyst **A** (10 mol%) and 5 Å MS. The results are summarized in Table 1. First, the reaction of enone **1a** (1.5 equiv.) with *rac*-**2** was allowed to react at −40°C to evaluate the degree of kinetic resolution of transetherified enone (*R*,*S*)-**3** in the step of cyclization (entries 1–3). After 24 h, two diastereomers (2*R*,2*S*)-**4** and (2*S*)-**5** [(2*R*,2*S*)-**4**:(2*S*)-**5** = 83:17, (2*R*)-**4** (94% ee)] as a mixture and another diastereomer (2*S*)-**6** were obtained in 50% and 7% yields, respectively. In addition, unreacted transetherified enone (*S*)-**3** (27%, 96% ee) was also obtained as the only *E*-isomer (entry 1). It took 60 h at −40°C to complete the cyclization of mismatching enone (*S*)-(*E*)-**3** affording the corresponding cycloadducts (entries 2 and 3). The absolute configuration and enantiomeric excess of unreacted enone **3** were determined as (*S*)-(*E*)-**3** after conversion to single diastereomeric cycloadduct (2*R*,2*S*)-**4** with $Cu(OTf)_2$ (10 mol%) as mentioned above. The results indicate that the cyclization of the matching pair (*R*)-(*E*)-**3** is faster than that of the mismatching pair (*S*)-(*E*)-**3** due to the discrimination effect of chiral catalyst **A**.



Scheme 2.

Table 1. Chiral Lewis acid-catalyzed double asymmetric induction during the tandem transetherification–intramolecular hetero Diels–Alder reaction of **1** with *rac*-**2**[a]



Entry	Enone **1a**, **b**	*rac*-**2** (equiv.)	Temp. (°C)	Time (h)	Yields of cycloadducts (%)[b,c]		Ratio of 2*R*-**4**/2*S*-**4**–**6**	% ee of[c] (2*R*)-**4**
					(2*R*,2*S*)-**4**+(2*S*)-**5**	(2*S*)-**6**		
1[d,e]	**1a**	1	−40	24	50 (83:17)	<7	71/29	94
2[d,e]	**1a**	1	−40	48	58 (70:30)	8	55/45	78
3[d]	**1a**	1	−40	60	67 (59:41)	9	45/55	72
4[d]	**1b**	1	−20	6	79 (61:39)	7	50/50	78
5	**1a**	2	rt	0.5	61 (70:30)	10	54/46	80
6	**1a**	2	0	2	65 (85:15)	4	76/24	90
7	**1a**	2	−20	14	63 (90:10)	3	86/14	96
8	**1a**	2	−40	36	73 (94: 6)	<2	90/10	96
9	**1a**	2	−60	96	66 (96: 4)	0	95/5	97
10	**1a**	2	−40	24	80 (96: 4)	<1	93/7	97
11	**1a**	2	−40	48	68 (93: 7)	<3	85/15	93

[a] All reactions were performed with 10 mol% of catalyst **A** [(*S*,*S*)-*t*-Bu-Box-Cu(S_bF_6)$_2$] in CH_2Cl_2 in the presence of 5 Å MS. The only one cycloadduct (2*R*)-**4** and three diastereomeric cycloadducts (2*S*)-**4**–**6** were obtained by the reaction with (*R*)-**2** and (*S*)-**2**, respectively.

[b] Isolated yields as a mixture of diastereomeric cycloadducts (2*R*,2*S*)-**4** and (2*S*)-**5**. The ratio in parentheses was determined by ^{1}H NMR analysis. Cycloadduct (2*S*)-**6** was isolated as a single diastereomer.

[c] The enantiomeric excesses of (2*R*)-**4** (72–97% ee), (2*S*)-**5** (>99% ee), and (2*S*)-**6** (>99% ee) were determined by chiral HPLC (DAICEL CHIRALCEL OD-H) analysis.

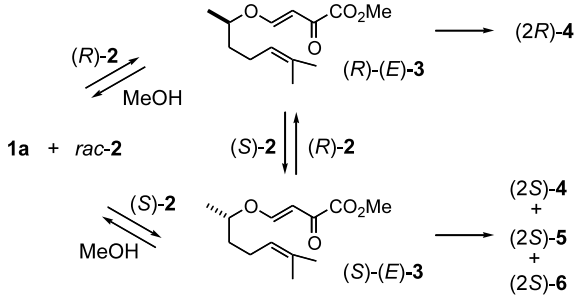
[d] 1.5 equiv. of enone **1** was used.

[e] Enone (*S*)-(*E*)-**3** was obtained in 27% (96% ee) and 17% (96% ee) yields, respectively.

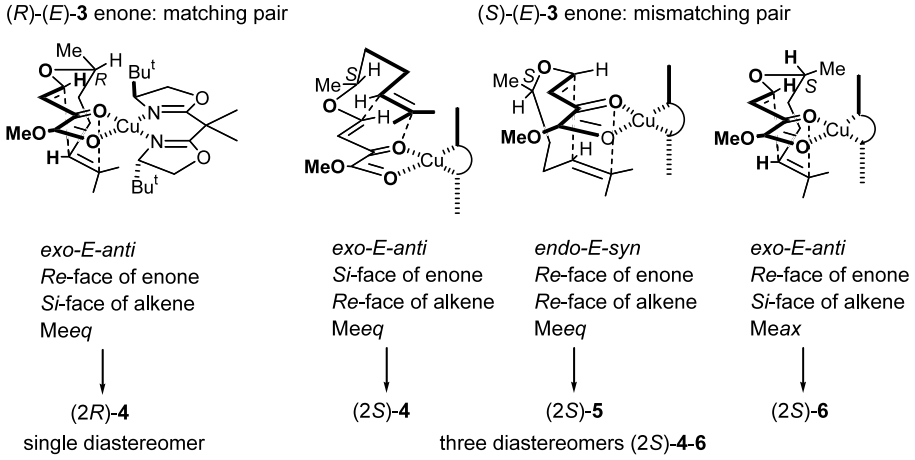
The effective double asymmetric induction during the tandem reaction could be expected by the formation of a sufficient amount of the matching enone (*R*)-(*E*)-**3** under the rapid reversible transetherification of both enone **1a** and *rac*-(*E*)-**3** with an excess of *rac*-**2**. The existence of direct transetherification of enone *rac*-(*E*)-**3** and *rac*-**2** in the reaction pathway was proved by the following model reaction with *sec*-alkoxy-substituted methyl (*E*)-4-(2-pentyloxy)-2-oxo-3-butenoate (**1b**), which was prepared as the only *E*-isomer by thermal transetherification of **1a** with 2-pentanol in 75%. Chiral Lewis acid-catalyzed tandem reaction of enone **1b** with *rac*-**2** proceeded smoothly within 6 h at −20°C to provide the corresponding cycloadducts [(2*R*,2*S*)-**4**+(2*S*)-**5** (79%, 61:39), (2*R*)-**4** (78% ee) and (2*S*)-**6** (7%)] in combined yield of 86% (entry 4).

Therefore, the tandem reaction of enone **1a** with 2 equiv. of alcohol *rac*-**2** was carried out until the completion of reaction in the range of room temperature to −40°C under the same catalytic system (entries 5–8). The only one cycloadduct (2*R*)-**4** arising from (*R*)-**2** and three diastereomeric cycloadducts (2*S*)-**4**–**6** arising from (*S*)-**2** were obtained in good combined yields (66–75%). At −60°C, the formation of cycloadduct (2*S*)-**6** was not observed (entry 9). The results indicate that the kinetic resolution of enone (*R*,*S*)-(*E*)-**3** [(2*R*)-**4**/(2*S*)-**4**–**6**] and the enantioselectivity of cycloadduct (2*R*)-**4** are effectively improved by lowering the reaction temperature as follows: 54/46 and 80% ee (room temperature), 76/24 and 90% ee (0°C), 84/16 and 96% ee (−20°C), 90/10 and 96% ee (−40°C), 95/5 and 97% ee (−60°C) (entries 5–9). The reaction of **1a** with 3 equiv. of *rac*-**2** at −40°C gave a slightly better result than with 2 equiv. of *rac*-**2** [81% combined yields, (2*R*)-**4**/(2*S*)-**4**-**6**=93/7, (2*R*)-**4** (97% ee)] (entry 10 versus entry 8). The reaction of enone **1b** with *rac*-**2** (2 equiv.) also proceeded at −40°C to afford the corresponding cycloadducts in combined yield of 71% with reasonable kinetic resolution [(2*R*)-**4**/(2*S*)-**4**–**6**=85/15] and high enantioselectivity of (2*R*)-**4** (93% ee) (entry 11).

The proposed pathway of the tandem reaction of enone **1a** with *rac*-**2** is shown in Scheme 3. Furthermore, the possible transition structures (TS-**A**-**D**) with conforma-



Scheme 3.



Scheme 4.

tion of a chairlike arranged tether in cyclization of (*R*,*S*)-(*E*)-**3** leading to the corresponding diastereomeric cycloadducts (2*R*)-**4** and (2*S*)-**4**–**6** are described on the basis of a square-planar intermediate by coordination of the vicinal carbonyl functionalities of (*R*,*S*)-(*E*)-**3** with the copper(II) center in bidentate fashion (Scheme 4).

In summary, we have successfully achieved an effective double asymmetric induction during the tandem transetherification–intramolecular hetero Diels–Alder reaction of enone **1a** with excess of *rac*-**2** using (*S*,*S*)-*t*-Bu-bis(oxazoline)-Cu(SbF_6)$_2$ **A** as a catalyst in the presence of 5 Å MS. To the best of our knowledge, this is a new methodology for the catalytic asymmetric intramolecular hetero Diels–Alder reaction. Studies on additional application of this type of asymmetric induction are in progress.

Acknowledgements

Partial financial support by a Grant-in-Aid for Scientific Research (no. 11640540) from the Japanese Ministry of Education, Science, Sports and Culture is acknowledged.

References

1. *Comprehensive Asymmetric Catalyst I–III*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999.
2. (a) Narasaka, K.; Hayashi, Y.; Shimada, S. *Chem. Lett*. **1988**, 1609–1612; (b) Tietz, L. F.; Saling, P. *Synlett* **1992**, 281–282; (c) Tietz, L. F.; Saling, P. *Chirality* **1993**, *5*, 329–333.
3. (a) Ho, T.-L. *Tandem Organic Reaction*; John Wiley: New York, 1992; (b) Tietz, L. F. *Chem. Rev*. **1996**, *96*, 115–136; (c) Denmark, S. K. *Chem. Rev*. **1996**, *96*, 137–169; see also: (d) Inoue, S.; Asami, M.; Honda, K.; Miyazaki, H. *Chem. Lett*. **1996**, 889–890; (e) Wada, E.; Kumaran, G.; Kanemasa, S. *Tetrahedron Lett*. **2000**, *41*, 73–76; (f) Miyazaki, H.; Honda, K.; Inoue, S. *Tetrahedron Lett*. **2000**, *41*, 2643–2646; (g) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans 1*. **2001**, 2303–2340.
4. Wada, E.; Koga, H.; Kumaran, G. *Tetrahedron Lett*. **2002**, *43*, 9397–9400.
5. Asymmetric intermolecular hetero Diels–Alder reaction with bis(oxazoline) copper(II) complex: (a) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc*. **1998**, *120*, 4895–4896; (b) Thorhauge, J.; Johansen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **1998**, *37*, 2404–2406; (c) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed*. **1998**, *37*, 3372–3375; (d) Evans, D. A.; Johnson, J. S.; Burgey, C. S. *Tetrahedron Lett*. **1999**, *40*, 2879–2882; (e) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem*. **2000**, *65*, 4487–4497; (f) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc*. **2000**, *122*, 1635–1649.
6. (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed*. **1985**, *24*, 1–76; (b) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc*. **1999**, *121*, 8251–8259 and references cited therein.
7. Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500–508.
8. ^{1}H NMR (600 MHz) spectral data for (2*S*)-**4**–**6** are as follows: (2*S*)-**4** ($CDCl_3$) $\delta=1.15$ (3H, s, one of 5-Me), 1.23 (3H, d, $J=6.2$ Hz, 2-Me), 1.27 (1H, dq, $J_{4ax-3eq}=3.7$ and $J_{4ax-3ax}=J_{4ax-4a}=J_{gem}=12.3$ Hz, H-4ax), 1.33–1.43 (1H, m, H-3ax), 1.40 (3H, s, the other of 5-Me), 1.49 (1H, ddd, $J_{4a-4eq}=3.2$, $J_{4a-8a}=10.1$, and $J_{4a-4ax}=12.3$ Hz, H-4a), 1.76 (1H, dddd, $J_{3eq-2}=2.2$, $J_{3eq-4eq}=3.2$, $J_{3eq-4ax}=3.7$ and $J_{gem}=13.0$ Hz, H-3eq), 1.83 (1H, dq, $J_{4eq-3ax}=J_{4eq-3eq}=J_{4eq-4a}=3.2$, and $J_{gem}=12.3$ Hz, H-4eq), 3.59 (1H, ddq, $J_{2-3eq}=2.2$, $J_{2-2-Me}=6.2$, and $J_{2-3ax}=12.4$, Hz, H-2), 3.77 (3H, s, 7-CO_2Me), 3.82 (1H, dd, $J_{8a-4a}=10.1$ and $J_{8a-8}=1.8$ Hz, H-8a), 6.00 (1H, d, $J_{8-8a}=1.7$ Hz, H-8); (2*S*)-**5** [as a mixture of (2*S*)-**4**, $CDCl_3$] $\delta=1.15$ (3H, d, $J_{2-Me-2}=6.2$ Hz, 2-Me), 1.18–1.27 (1H, m, H-3ax), 1.24 (3H, s, one of 5-Me), 1.33 (1H, dq, $J_{4ax-3eq}=3.9$ and $J_{4ax-4a}=J_{4a-3ax}=J_{gem}=13.2$ Hz, H-4ax), 1.37 (3H, s, the other of 5-Me), 1.36–1.41 (1H, m, H-3eq), 1.59–1.65 (1H, m, H-4a), 1.76–1.81 (1H, m, H-4eq), 3.55 (1H, ddq. $J_{2-3eq}=1.6$, $J_{2-2-Me}=6.2$, and $J_{2-3ax}=12.1$ Hz, H-2), 3.8 (3H, s, 7-CO_2Me), 4.69 (1H, dd, $J_{8a-8}=1.1$ and $J_{8a-4a}=6.1$ Hz, H-8a), 5.98 (1H, t,

$J_{8-8a} = J_{8-4a} = 1.1$ Hz, H-8); (2*S*)-**6** (C_6D_6) $\delta = 0.91$ (3H, s, one of 5-Me), 0.93 (1H, dq, $J_{4ax-3eq} = 3.1$ and $J_{4ax-3ax} = J_{4ax-4a} = J_{gem} = 12.6$ Hz, H-4ax), 1.01 (3H, d, $J = 6.8$ Hz, 2-Me), 1.05–1.13 (2H, m, one of H-3 and H-4eq), 1.15 (3H, s, the other of 5-Me), 1.43 (1H, ddd, $J_{4a-4eq} = 2.9$, $J_{4a-8a} = 10.1$, and $J_{4a-4ax} = 12.6$ Hz, H-4a), 1.52–1.60 (1H, m, the other of H-3), 3.33 (3H, s, 7-CO2Me), 3.98 (1H, dd, $J_{8a-8} = 2.0$ and $J_{8a-4a} = 10.1$ Hz, H-8a), 4.07 (1H, quintet, $J_{2-2-Me} = J_{2-3eq} = 6.7$ Hz, H-2) and 6.30 (1H, d, $J_{8-8a} = 2.0$ Hz, H-8).