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Synthesis of novel simplified eleutheside analogues with potent microtubule-stabilizing activity, using ring-closing metathesis as the key-step

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Abstract—The synthesis of a number of novel simplified eleutheside analogues with potent tubulin-assembling and microtubule-stabilizing properties is described, using ring-closing metathesis as the key-step for obtaining the 6–10 fused bicyclic ring system.

Sarcodictyins A and B **1** and eleutherobin **2** (the 'eleutheside' family of microtubule-stabilizing agents, Fig. 1) are active against paclitaxel-resistant tumor cell lines and therefore hold potential as second generation microtubule-stabilizing anticancer drugs.[1] The scarce availability of **1** and **2** from natural sources makes their total syntheses vital for further biological investigations.[1] To date, sarcodictyins A and B have been synthesized successfully by Nicolaou et al.,[2] who have also exploited a similar route for accessing eleutherobin.[3] A subsequent report by Danishefsky and co-workers detail an elegant alternative access to eleutherobin.[4] A number of partial syntheses and approaches have also been described.[5]

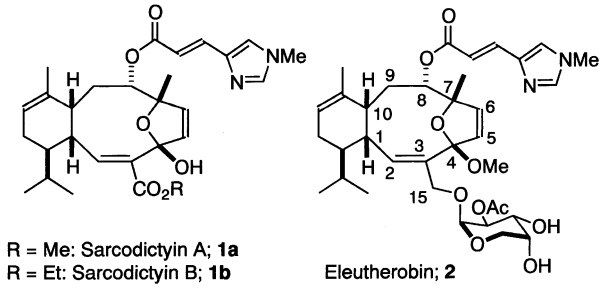

Figure 1. Marine diterpenoids sarcodictyin A (**1a**), B (**1b**) and eleutherobin (**2**).

The total syntheses of the eleuthesides have generated very limited diversity in the diterpenoid core, with major variations reported only in the C-15 functionality and C-8 side-chain.[1–4] In a recent communication,[5h] we described the transformation of aldehyde **3** (prepared in 6 steps on a multigram scale from *R*-(−)-carvone in 30% overall yield)[5a,g] into the RCM precursor **8** via multiple stereoselective Brown allylations[6] (Scheme 1). Diene **8** was subjected to ring-closing metathesis (RCM)[7] using the 'second generation' RCM-catalysts[8] **10** and **11** to give the desired ring-closed product **9** as a single *Z* stereoisomer in $\geq 80\%$ yield.[5h]

As part of our ongoing program aimed at the synthesis of simplified analogues of the eleutheside natural products, ideally showing improved synthetic accessibility and retaining microtubule-stabilizing properties, we describe in this Letter the synthesis of a number of eleutheside analogues with potent tubulin-assembling and microtubule-stabilizing activity, using RCM as the key-step for obtaining the 6–10 fused bicyclic ring system. A first set of eleutheside analogues (**12**, **14** and **16**) was synthesized from compound **9** using standard, high-yielding transformations (Scheme 2).[9]

Keywords: allylation; antitumour compounds; metathesis; stereocontrol.

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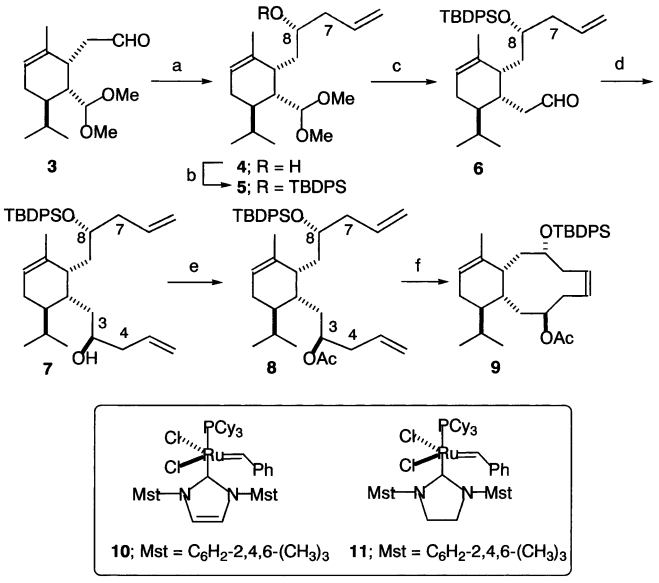
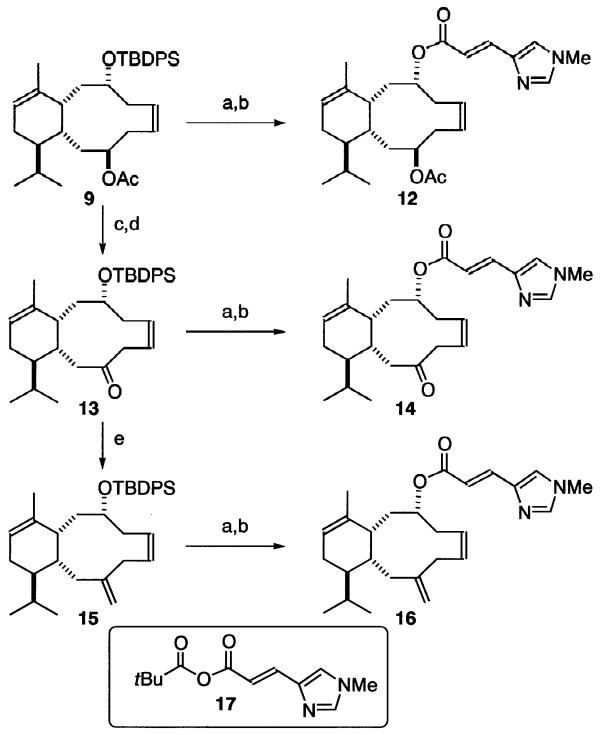


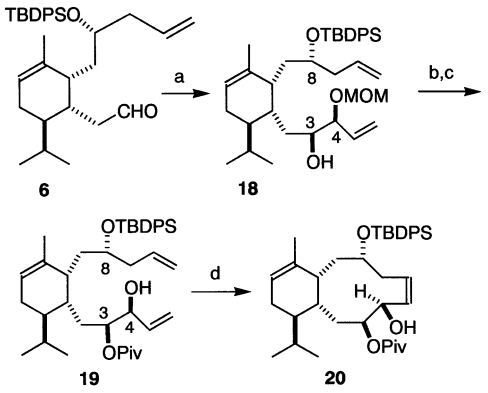
Scheme 1. *Reagents and conditions*: (a) i. AllMgBr, $^{l}Ipc_2BOMe$, Et_2O–THF, 0°C to rt; ii. **3**, −78°C to rt, 6 h; iii. 6N NaOH, H_2O_2, rt, 15 h, 77% (>95% diastereomeric purity). (b) TBDPS-Cl, excess imidazole, CH_2Cl_2, rt, 16 h, 99%. (c) i. AcOH: THF: H_2O (3:1:1), rt, 16 h, 99%; ii. $NaBH_4$, EtOH, rt, 15 min, 98%; iii. MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 1 h, 99%; iv. KCN, 18-crown-6, MeCN, 80°C, 5 h, 95%; v. DIBAl-H, hexane–toluene (2:1), −78°C, 40 min, 99%. (d) i. AllMgBr, $^{l}Ipc_2BOMe$, Et_2O–THF, 0°C to rt; ii. **6**, −78°C to rt, 2 h; iii. 6N NaOH, H_2O_2, rt, 15 h, 55% (>95% diastereomeric purity). (e) Ac_2O, cat. DMAP, Py, rt, 94%. (f) **10** (30% mol), CH_2Cl_2, rt, 24 h, 80% (100% *Z*), or **11** (7% mol), CH_2Cl_2, rt, 168 h, 88% (95% after recovering starting material, 100% *Z*).

Aldehyde **6** was oxyallylated using Brown's methodology [(*Z*)-γ-(methoxymethoxy)allyldiisopinocampheylborane from (−)-α-pinene][6d] in high yield (77%) and with good stereoselectivity (3*S*,4*S*:3*R*,4*R*=91:9, Scheme 3). The major diastereomer **18** was isolated by flash chromatography and transformed into the allylic alcohol **19** via a simple protection/deprotection sequence. 'Second generation' Grubbs' catalyst **11** gave the desired ring-closed product **20** as a single *Z* stereoisomer in 73% yield. As expected, entropic support (by virtue of the *cis* fusion to the cyclohexyl ring) made ring closure of diene **19** extremely smooth. Luckily, and delightfully, the stereochemistry of the double bond created by the RCM reaction was fully controlled in the desired sense (100% *Z*) by the structure of the new ten-membered ring.[10] The stereochemical course likely reflects thermodynamic control.[11] The crucial role of the protecting groups in the cyclization precursor **19** is noteworthy: (a) the large TBDPS group in position 8 helps to suppress the undesired dimerization reaction;[12] (b) a free allylic alcohol[13] in position 4 is necessary to promote the cyclization (the RCM reaction did not occur on dienes with variously protected allylic alcohols in position 4).[14]

Compound **20** was transformed into a second set of eleutheside analogues **21**–**23**, using standard, high-yielding transformations (Scheme 4).[9]

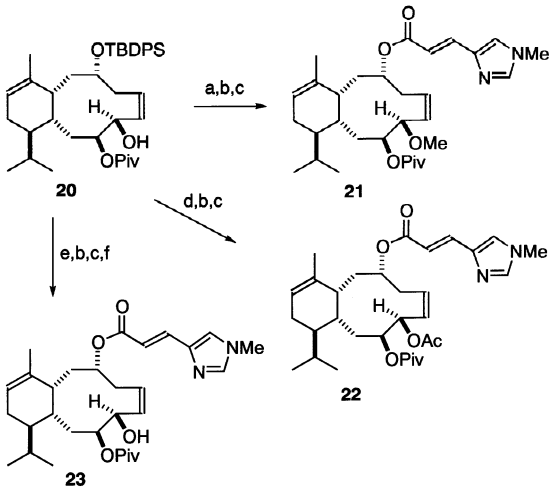


Scheme 2. *Reagents and conditions*: (a) TBAF, THF, rt, 94–100%. (b) **17** (Ref. 2b), Et_3N, DMAP, CH_2Cl_2, 50–59%. (c) K_2CO_3, MeOH, 94%. (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 to 0°C, 90%. (e) $Ph_3P{=}CH_2$, THF, 50°C, 92%.

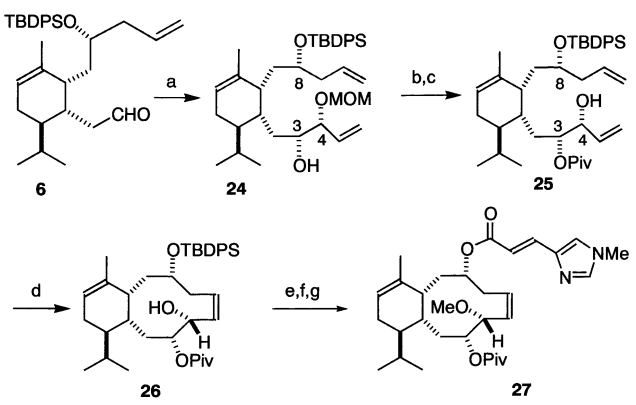


Scheme 3. *Reagents and conditions*: (a) i. $^{l}Ipc_2BOMe$, AllOMOM, *s*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78°C; ii. 6N NaOH, H_2O_2, rt, 15 h, 77% (91% diastereomeric purity). (b) *t*-BuCOCl (PivCl), cat. DMAP, Py, rt, 80%. (c) $BF_3{\cdot}Et_2O$, PhSH, CH_2Cl_2, −78 to −10°C, 64%. (d) **11** (10% mol), CH_2Cl_2, rt, 120 h, 73% (100% *Z*).

Aldehyde **6** was also oxyallylated using Brown's enantiomeric reagent [(*Z*)-γ-(methoxymethoxy)allyldiisopinocampheylborane from (+)-α-pinene][6d] in high yield (76%) and with excellent stereoselectivity (3*R*,4*R*:3*S*,4*S*=97.4:2.6, Scheme 5). The major diastereomer **24** was isolated by flash chromatography and transformed into the allylic alcohol **25** via a simple protection/deprotection sequence (in this case Me_2S, $BF_3{\cdot}Et_2O$ proved more reliable than PhSH, $BF_3{\cdot}Et_2O$ for deprotecting the allylic alcohol from the MOM group).[15]



Scheme 4. *Reagents and conditions*: (a) MeOTf, 2,6-di-*t*-Bu-Py, CH_2Cl_2, 40°C, 96%. (b) TBAF, THF, rt, 89–100%. (c) **17** (Ref. 2b), Et_3N, DMAP, CH_2Cl_2, 61–80%. (d) Ac_2O, cat. DMAP, Py, rt, 71%. (e) DHP, PPTS, CH_2Cl_2, 77%. (f) PTSA, EtOH: H_2O (8:2), 82%.



Scheme 5. *Reagents and conditions*: (a) i. $^{d}Ipc_2BOMe$, AllO-MOM, *s*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78°C; ii. H_2O_2, 6N NaOH, rt, 15 h, 76% (97.4% diastereomeric purity). (b) *t*-BuCOCl (PivCl), cat. DMAP, Py, rt, 94%. (c) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, −20°C, 78%. (d) **11** (10% mol), CH_2Cl_2, rt, 120 h, 60% (100% *Z*). (e) MeOTf, 2,6-di-*t*-Bu-Py, CH_2Cl_2, 40°C, 99%. (f) TBAF, THF, rt, 67%. (g) **17** (Ref. 2b), Et_3N, DMAP, $ClCH_2CH_2Cl$, 79%.

Treatment with catalyst **11** gave the desired ring-closed product **26** as a single *Z* stereoisomer in 60% yield. Finally, a standard sequence of reactions transformed compound **26** into the eleutheside analogue **27**.[9]

The effect of these new eleutheside analogues on the assembly of tubulin was assessed at Pharmacia (Nerviano, Italy) and at Salford (UK), using paclitaxel as a reference (Table 1).

Eleutheside analogue **14** was shown to be at least as potent as paclitaxel. Microtubules were generated in the presence of $CaCl_2$ and were stable (did not depolymerize) at 10°C. Although there is a general agreement that the (*E*)-*N*-methylurocanic side chain, the C-4/C-7 ether bridge, and the cyclohexene ring are important determinants of antimitotic activity,[1] it is interesting to note that these simplified analogues of the natural product (lacking inter alia the C-4/C-7 ether bridge) retain potent microtubule stabilizing activity. Given the dramatic impact that the furanose oxygen deletion is likely to have on the conformation of the ring system, the fact that some of these compounds retain activity comparable to paclitaxel in the tubulin polymerization assay is remarkable. Work is in progress to synthesize more potent eleutheside analogues, investigate the interaction with tubulin and establish their cytotoxicity.

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Table 1. Tubulin polymerizing activities[a]

Compound	ED_{50} (μM)	ED_{90} (μM)	Paclitaxel ED_{50} (μM)	Paclitaxel ED_{90} (μM)
12	2.0	10.0	<0.5	0.5
14	0.2	1.2	0.5	3.0
16	5.0	16.0	<0.5	0.5
21	3.0	7.0	0.5	3.0
22	1.0	1.7	<0.5	0.5
23	1.0	1.8	<0.5	0.5
27	n.d.[b]	n.d.[b]	–	–

[a] ED_{50} = effective dose that induces 50% tubulin polymerization; ED_{90} = effective dose that induces 90% tubulin polymerization (see: Battistini, C.; Ciomei, M.; Pietra, F.; D'Ambrosio, M.; Guerriero, A. (Pharmacia), PCT Int. Appl. WO 96 36,335, 1996 [*Chem. Abstr.* **1997**, 126, P54863x]). ED values may vary depending on the tubulin batch (from pig brain): the same batch is used for the paclitaxel reference assay.

[b] Not determined: the compound precipitates at 1.0 μM concentration, under the ED_{50} value.

References

1. For a comprehensive review on the chemistry and biology of the sarcodictyins, see: (a) Nicolaou, K. C.; Pfefferkorn, J.; Xu, J.; Winssinger, N.; Ohshima, T.; Kim, S.; Hosokawa, S.; Vourloumis, D.; van Delft, F.; Li, T. *Chem. Pharm. Bull.* **1999**, *47*, 1199. See also: (b) Nicolaou, K. C.; Winssinger, N.; Vorloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J. Y.; Li, T. *J. Am. Chem. Soc.* **1998**, *120*, 10814; (c) Britton, R.; de Silva, E. D.; Bigg, C. M.; McHardy, L. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 8632 and references cited therein.
2. (a) Nicolaou, K. C.; Xu, J.-Y.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353; (b) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661; (c) Nicolaou, K. C.; Kim, S.; Pfefferkorn, J.; Xu, J.; Ohshima, T.; Hosokawa, S.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1418.
3. (a) Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520; (b) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674.
4. (a) Chen, X.-T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 185; (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 789; (c) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.
5. (a) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 153; (b) Baron, A.; Caprio, V.; Mann, J. *Tetrahedron Lett.* **1999**, *40*, 9321; (c) Carter, R.; Hodgetts, K.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56*, 4367; (d) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 6254; (e) Xu, Q.; Weeresakare, M.; Rainier, J. D. *Tetrahedron* **2001**, *57*, 8029; (f) Ceccarelli, S.; Piarulli, U.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 7421; (g) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57*, 8531; (h) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Monti, D.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 9187; (i) Sandoval, C.; Redero, E.; Mateos-Timoneda, M. A.; Bermejo, F. A. *Tetrahedron Lett.* **2002**, *43*, 6521.
6. (a) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065; (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092; (c) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432; (d) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535; (e) Brown, H. C.; Racherla, U. S.; Liao, Y.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608.
7. For reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371; (c) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073; (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.
8. (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674; (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247; (c) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375; (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953; (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
9. Compound **12**: $[\alpha]_D^{20}=-29.0$ (*c* 0.71, EtOAc); **14**: $[\alpha]_D^{20}=-15.6$ (*c* 0.34, EtOAc); **16**: $[\alpha]_D^{20}=+6.0$ (*c* 0.05, EtOAc); **21**: $[\alpha]_D^{20}=-17.0$ (*c* 0.33, EtOAc); **22**: $[\alpha]_D^{20}=-39.6$ (*c* 0.24, EtOAc); **23**: $[\alpha]_D^{20}=-45.0$ (*c* 0.28, EtOAc); **27**: $[\alpha]_D^{20}=-43.8$ (*c* 0.70, EtOAc). All compounds described in the present paper gave HRMS and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) completely in accord with their assigned structures. Details will be provided in a subsequent full paper.
10. Application of the RCM reaction to ten-membered carbocycles is still very rare, see: (a) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4060; *J. Org. Chem.* **2002**, *67*, 1554; (b) Ref. 5h.
11. The use of 'second generation' metathesis catalysts results in the selective formation of the thermodynamically favored stereoisomeric products in RCM reactions furnishing medium-sized rings, see: (a) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061; (b) Murga, J.; Falomir, E.; Garcìa-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447.
12. Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325.
13. Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.
14. For discussions on the role of allylic oxygen substituents in the RCM reaction, see: (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129; (b) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492; (c) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263.
15. (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662; (b) Sasaki, M.; Noguchi, T.; Tachibana, K. *J. Org. Chem.* **2002**, *67*, 3301.