# General synthesis of epi-series catechins and their 3-gallates: reverse polarity strategy†

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**A general synthetic route to the epi-series catechins was developed based on the reverse polarity strategy. Aromatic nucleophilic substitution reaction followed by the sulfinyl–metal exchange and cyclization enabled stereo-controlled access to various members of epi-series catechins and their 3-gallates.**

Recently, much attention has been centered on the significant bioactivities of the epi-series catechins as represented by tea catechins, *e.g.* (–)-epigallocatechin (EGC, **1**), (–)-epicatechin (EC, **2**), and (–)-epiafzelechin (EZ, **3**) (Fig. 1).[1] (–)-Epigallocatechin gallate (EGCg, **4**), one of the most abundant ingredients in green tea, exhibits remarkable suppressive effects against various human tumor cell lines, and also antimutagenic activity and antivirus effects.[2]

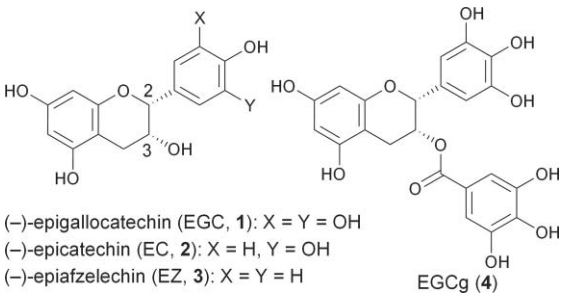
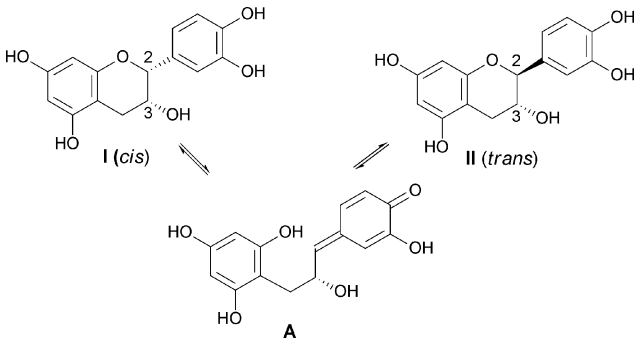



**Fig. 1** Structure of epicatechin-type polyphenols.

A recent study at the molecular level revealed the specific binding of **4** to the 67 kDa laminin receptor that mediates its anticancer action at physiologically relevant concentrations.[2c] Because of their relevance to these significant bio-functions, **4** and other epicatechin-3-gallate derivatives have attracted a great deal of scientific attention.

In spite of such promise, controlled synthesis of the epi-series catechins remains a challenge, due to chemical/stereochemical lability (Scheme 1): the C(2)-stereocenter is prone to epimerization (**I**⇄**A**⇄**II**) under basic/acidic conditions providing a variable mixture with the catechin congeners of 2,3-*trans* stereochemistry. Even racemization can take place *via*, *inter alia*, the enolization from **A**.[3]

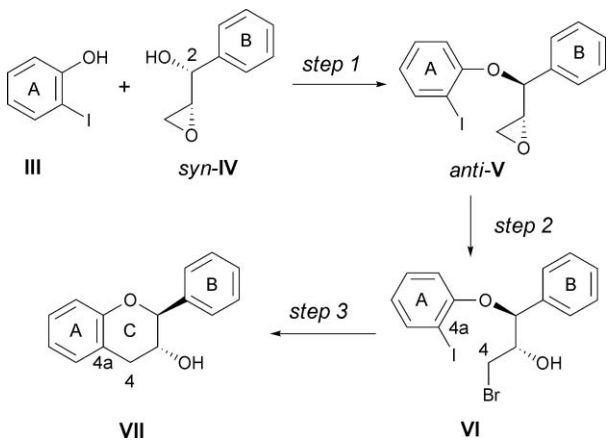
So far, preparation of the epicatechins mainly relies on the *inversion* of the C(3)-stereochemistry of the catechin derivatives *via*




**Scheme 1** Stereochemical lability of catechin/epicatechin derivatives.

oxidation and reduction,[4] which, however, inevitably depends on the availability of the catechin starting materials. Other approaches have started to appear, which, however, are still limited in scope in terms of the versatility or the accessibility of the single enantiomer.[5]

Recently, we reported a stereo-controlled synthetic approach to the *catechin* derivatives *via* three key steps (Scheme 2);[6] the Mitsunobu-type C–O bond formation[7] of iodophenol **III** and epoxy alcohol *syn*-**IV** (step 1), cleavage of the oxirane ring to give the corresponding bromohydrin **VI** (step 2), and the pyran-ring closure *via* the selective iodine–metal exchange, constructing the catechin skeleton **VII** (step 3). Ready availability of *syn*-**IV**[8] *via* Sharpless asymmetric dihydroxylation[9] makes this protocol a general route to various *catechin* derivatives.




**Scheme 2** Stereo-controlled approach to catechin derivatives.

We envisioned that such an approach could provide access to the *epicatechins* as well, given that the epimeric precursor *syn*-**V** was accessible (Scheme 3). Among several options for the preparation of the requisite structure *syn*-**V**,[10] we focused on a change in the

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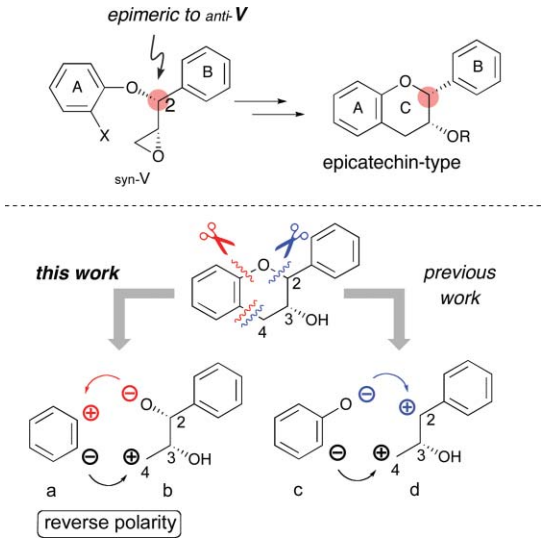
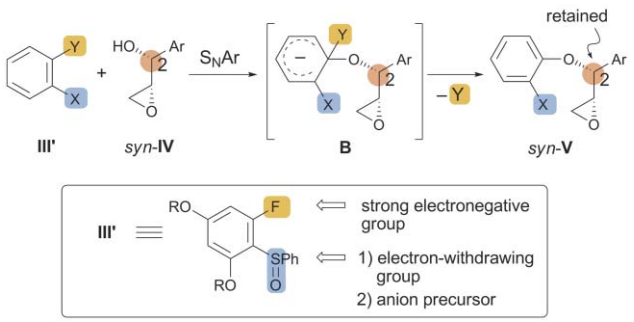



**Scheme 3** Change of the connectivity for reverse polarity strategy.

connectivity of the A/B-ring fragments: Instead of dissecting the C ring into fragments **c** and **d** (blue lines), disconnection at the Ar–O and Ar–C bonds (red lines) provides a new fragment pair, **a** and **b**, which could be combined *in a reversed polarity* (*umpolung*) *fashion* without affecting the C(2)-stereochemistry in **b**.

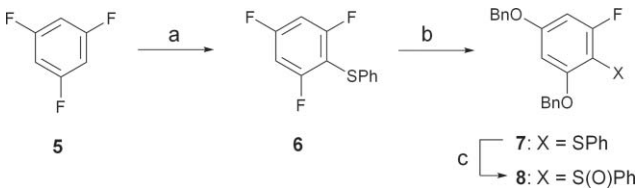
To realise this scenario, we planned the aromatic nucleophilic substitution ($S_NAr$)[11] by employing electrophilic unit **III′** and the alkoxide derived from *syn*-**IV** (Scheme 4).




**Scheme 4** $S_NAr$ strategy for retentive assembly of **III′** and *syn*-**IV**.

The choice of the two substituents X and Y was critical. The Y group has to be a strongly electronegative group such as fluorine, being capable of attracting the incoming nucleophile to form the Meisenheimer complex **B**. On the other hand, the X group must play two roles, (1) a π-electron acceptor to facilitate the conjugate attack, and (2) an anion precursor at the stage of the pyran-ring closure later in the synthetic scheme. We chose a *sulfinyl* group as X,[12] expecting that the sulfinyl–metal exchange[13] would serve for the latter purpose.

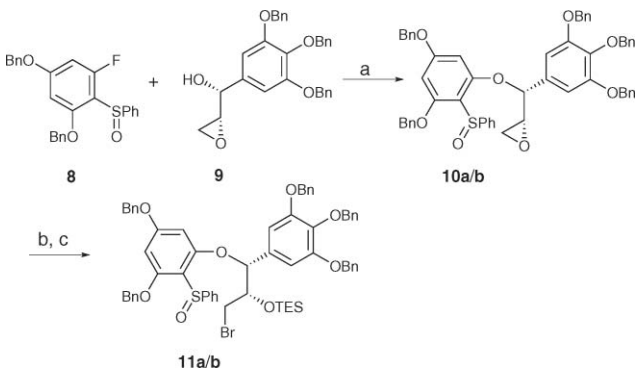
Scheme 5 shows the preparation of fluoro-sulfoxide **8**. Lithiation of 1,3,5-trifluorobenzene (**5**)[14] with *n*-BuLi[15] followed by trapping of the resulting anion with $PhSSO_2Ph$[16] gave sulfide **6** in 87% yield. Upon careful treatment of **6** with sodium benzyloxide (2.5 mol equiv., 0 °C, DMF, 1 h), two fluorine atoms were displaced with high regioselectivity, giving the 2,4-bis-benzyl ether **7**. A small amount of the 2,6-regioisomer was also produced which was inseparable at this stage. However, oxidation to the corresponding




**Scheme 5** Conditions: (a) *n*-BuLi, $PhSSO_2Ph$, $Et_2O$, −78 °C, 87%. (b) BnOH, NaH, DMF, 0 °C. (c) *m*CPBA, $CH_2Cl_2$, 0 °C, 2 steps 85%.

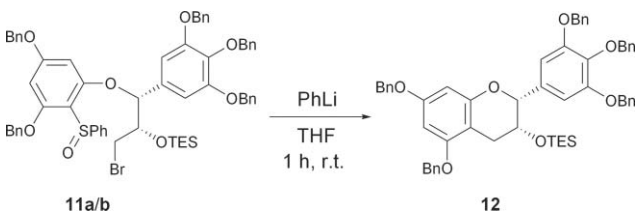
sulfoxides allowed isolation of **8** in 85% yield by silica-gel column chromatography (hexane–EtOAc = 4 : 1). The corresponding 2,6-regioisomer was separated in 8% yield.

With the requisite acceptor **8** in hand, the projected $S_NAr$ reaction was attempted (Scheme 6). Upon treatment of **8** with the sodium alkoxide of **9**,[6] the reaction proceeded smoothly in a mixed solvent (toluene–DMPU = 4 : 1) at 0 °C. Notably, the Payne rearrangement[17] was not observed under these conditions, thereby giving the desired $S_NAr$-product **10** in 76% yield as a mixture of diastereomers. Separation by silica-gel column chromatography gave diastereomeric epoxy ethers **10a** (39%) and **10b** (37%), albeit the sulfoxide stereochemistry was unspecified. Oxirane cleavage with $Li_2NiBr_4$[18] followed by silylation with triethylsilyl (TES) triflate afforded the diastereomeric bromides **11a/b** (97%: **11a** from **10a**, 91%: **11b** from **10b**), respectively.




**Scheme 6** Conditions: (a) NaH, toluene, DMPU room temp., 39% for **10a**, 37% for **10b**. (b) $Li_2NiBr_4$, THF, 0 °C. (c) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 2 steps, 97% for **11a**, 91% for **11b**. DMPU = *N*,*N*′-dimethylpropyleneurea, TES = triethylsilyl.

The next stage was to construct the flavan skeleton. We planned the cyclization of **11a/b** *via* the sulfinyl–metal exchange followed by intramolecular nucleophilic substitution (Scheme 7). Thus, upon treatment of diastereomeric sulfoxides **11a** and **11b** with PhLi (2.0 equiv in THF, room temp., 1 h),[19] smooth cyclization of the pyran ring occurred, giving a single cyclized product **12**, respectively (81% from **11a** and 62% from **11b**). The C(2) and C(3)



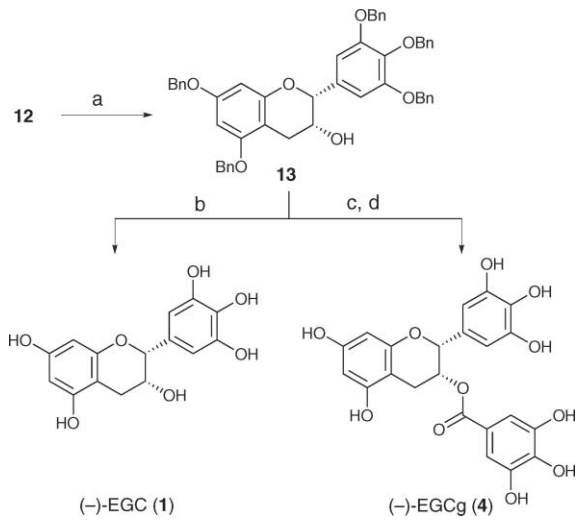

**Scheme 7** Construction of flavan skeleton by sulfur–metal exchange and intramolecular nucleophilic substitution.

relative stereochemistry was unambiguously assigned by $^1$H NMR analysis ($J_{2,3}$ = <0.5 Hz).

It is noteworthy that the aryl lithium species generated by the sulfinyl–metal exchange could be exploited for such an efficient C–C bond formation, which has sizable potential for application for other purposes.

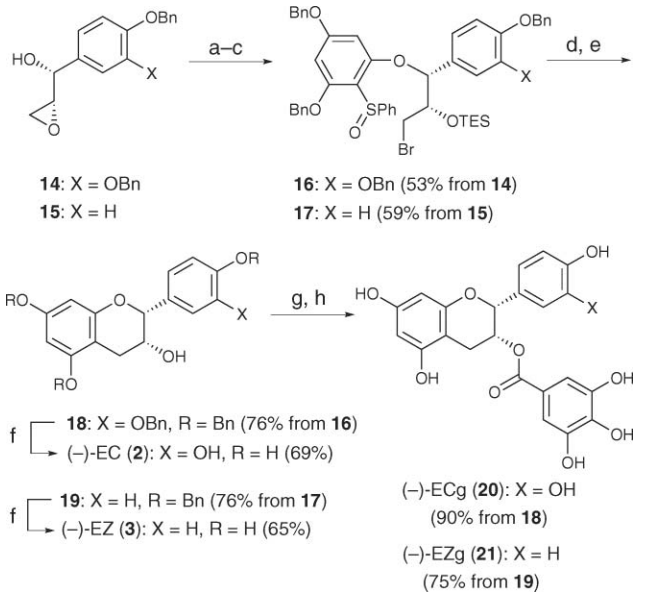
Conversion of **12** into EGC (**1**) was carried out as follows (Scheme 8). After removal of the TES group by *n*-$Bu_4NF$ to give alcohol **13**, all the benzyl protecting groups were removed by hydrogenolysis over 20% $Pd(OH)_2/C$ in a mixed solvent (THF–MeOH–$H_2O$ = 4 : 4 : 1, 12 h). Careful non-aerobic filtration through a Celite pad (washed with MeOH) followed by purification by Sephadex LH-20 column chromatography (MeOH) afforded (–)-EGC (**1**) as a snow-white amorphous solid (64% yield from **12**), which was indistinguishable from the authentic specimen in all respects {$[\alpha]_D^{21}$ −56.0 (*c* 1.02, acetone–$H_2O$ = 1 : 1), *lit*. $[\alpha]_D^{24}$ −57.1 (*c* 1, acetone–$H_2O$ = 1 : 1).[3c]




**Scheme 8** Conditions: (a) *n*-$Bu_4NF$, THF, 0 °C, 99%. (b) $H_2$, $Pd(OH)_2$, THF, MeOH, $H_2O$ (4 : 4 : 1), room temp., 71%. (c) 3,4,5-tri-*O*-benzylgallic acid, EDCI·HCl, DMAP, $Et_3N$, $CH_2Cl_2$ room temp. (d) $H_2$, $Pd(OH)_2/C$, THF, MeOH, $H_2O$ (4 : 4 : 1), room temp., 68% (2 steps).

Furthermore, the protection pattern of alcohol **13** is ideally suited for straightforward access to EGCg (**4**): Esterification of **13** with 3,4,5-tri-*O*-benzylgallic acid followed by hydrogenolysis of all benzyl groups gave **4** {$[\alpha]_D^{21}$ −218 (*c* 0.660, acetone–$H_2O$ = 1 : 1), *lit*.[3c] $[\alpha]_D^{24}$ −216.4 (*c* 1, acetone–$H_2O$ = 1 : 1)} as a snow-white amorphous solid in good yield.

Starting from epoxy alcohols **14** and **15**, applicability of these protocols was further demonstrated by the syntheses of (–)-EC (**2**) and (–)-EZ (**3**), and its 3-gallates, respectively (Scheme 9). After the same three-step sequence as before, the resulting bromides **16** and **17**[20] were subjected to the cyclization followed by desilylation as before, giving the corresponding pyrans, **18** and **19** in good yield, respectively. Detachment of all the benzyl groups in **18** and **19** gave (–)-EC (**2**)[21] and (–)-EZ (**3**)[22] as a snow-white amorphous solid, respectively. Furthermore, esterification of **18** and **19** with 3,4,5-tri-*O*-benzylgallic acid followed by hydrogenolysis of all the benzyl groups gave the 3-gallate of (–)-epicatechin [(–)-ECg (**20**)],[23] and that of (–)-epiafzelechin [(–)-EZg (**21**)],[24] in good yields, respectively.




**Scheme 9** Synthesis of (–)-epicatechin [EC (**2**)] and (–)-epiafzelechin [EZ (**3**)] and their 3-gallates, (–)-ECg (**20**) and (–)-EZg (**21**). Conditions: (a) NaH, toluene, DMPU, room temp. (b) $Li_2NiBr_4$, THF, 0 °C. (c) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C. (d) PhLi, THF, 0 °C. (e) *n*-$Bu_4NF$, THF, 0 °C, 99%. (f) $H_2$, $Pd(OH)_2$, THF, MeOH, $H_2O$ (4 : 4 : 1), room temp.; (g) 3,4,5-tri-*O*-benzylgallic acid, EDCI·HCl, DMAP, $Et_3N$, $CH_2Cl_2$ room temp., (h) $H_2$, $Pd(OH)_2/C$, THF, MeOH, $H_2O$ (4 : 4 : 1), room temp. DMPU = *N*,*N*′-dimethylpropyleneurea, TES = triethylsilyl.

In summary, the work described above entails a number of noteworthy developments, including 1) the general and stereoselective access to the epi-series catechins and their 3-gallates, 2) the retentive assembly of the cyclization precursors *via* the nucleophilic aromatic substitution of aryl fluoride bearing a sulfinyl group at the *ortho* position, 3) the sulfinyl–metal exchange and following nucleophilic substitution to form the corresponding cyclized product. The efficient C–C bond formation in this process was especially striking, which should be useful for other purposes.

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## Notes and references

1 (*a*) J. Jankun, S. H. Selman and R. Swiercz, *Nature*, 1997, **387**, 561; (*b*) Y. Hara, *Green Tea*, CRC Press, Boca Raton, 2001.
2 (*a*) J.-M. Song, K.-H. Lee and B.-L. Seong, *Antiviral Res.*, 2005, **68**, 66; (*b*) M. Nakayama, K. Suzuki, M. Toda, S. Okubo and T. Shimamura, *Antiviral Res.*, 1993, **21**, 289; (*c*) H. Tachibana, K. Koga, Y. Fujimura and K. Yamada, *Nat. Struct. Mol. Biol.*, 2004, **11**, 380.
3 (*a*) A. J. Birch, J. W. Clark–Lewis and A. V. Robertson, *J. Chem. Soc.*, 1957, 3586; (*b*) P. Kiatgrajai, J. D. Wellons, L. Gollob and J. D. White, *J. Org. Chem.*, 1982, **47**, 2910; (*c*) R. Seto, H. Nakamura, F. Nanjo and Y. Hara, *Biosci., Biotechnol., Biochem.*, 1997, **61**, 1434; (*d*) P. P. Mehta and W. E. Whalley, *J. Chem. Soc.*, 1963, 5327.

4 W. Tückmantel, A. P. Kozikowski and L. J. Romanczyk, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 12073.
5 Syntheses of epi-series catechins, see: (*a*) L. Li and T. H. Chan, *Org. Lett.*, 2001, **3**, 739; (*b*) M. Kitade, Y. Ohno, H. Tanaka and T. Takahashi, *Synlett*, 2006, **17**, 2827; (*c*) H. Tanaka, H. Miyoshi, Y.-C. Chuang, Y. Ando and T. Takahashi, *Angew. Chem., Int. Ed.*, 2007, **46**, 5934; (*d*) T. Furuta, Y. Hirooka, A. Abe, Y. Sugata, M. Ueda, K. Murakami, T. Suzuki, K. Tanaka and T. Kan, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3095.
6 T. Higuchi, K. Ohmori and K. Suzuki, *Chem. Lett.*, 2006, **35**, 1006.
7 O. Mitsunobu, *Synthesis*, 1981, 1.
8 X. Ren, X. Chen, K. Peng, X. Xie, Y. Xia and X. Pan, *Tetrahedron: Asymmetry*, 2002, **13**, 1799.
9 K. B. Sharpless, W. Amberg, Y. L. Bennni, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu and X. L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
10 Two optional approaches are conceivable: 1) employment of the C(2)-epimer, *anti*-**IV**, as a substrate for the Mitsunobu reaction, 2) double inversion at the C(2) position. However, these approaches were less attractive in view of the poor accessibility of the substrate and/or the longer steps.
11 (*a*) G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, 1977, **10**, 125; (*b*) M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667; (*c*) J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968.
12 (*a*) A. M. Ratz and L. O. Weigel, *Tetrahedron Lett.*, 1999, **40**, 2239; (*b*) K. Hiroi, Y. Suzuki, I. Abe and R. Kawagishi, *Tetrahedron*, 2000, **56**, 4701.
13 (*a*) T. Durst, M. J. LeBelle, R. V. Elzen and K.-C. Tin, *Can. J. Chem.*, 1974, **52**, 761. For reviews, see: (*b*) S. Oae, *Rev. Heteroatom Chem.*, 1991, **4**, 195; (*c*) T. Satoh, *J. Synth. Org. Chem. Jpn.*, 1996, **54**, 481; (*d*) T. Satoh, *Farumashia*, 1999, **35**, 1225.
14 A. Pleschke, A. Marhold, M. Schneider, A. Kolomeitsev and G.-V. Roschenthaler, *J. Fluorine Chem.*, 2004, **125**, 1031.
15 (*a*) C. Heiss, E. Marzi, M. Florence and M. Schlosser, *Eur. J. Org. Chem.*, 2007, 669; (*b*) K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568; (*c*) M. Stratekis, P. G. Wang and A. Streitwieser, *J. Org. Chem.*, 1996, **61**, 3145.
16 F. Chemla, *Synlett*, 1998, 894.
17 (*a*) G. B. Payne, *J. Org. Chem.*, 1962, **27**, 3819; (*b*) R. M. Hanson, *Org. React.*, 2002, **60**, 1.
18 R. D. Dawe, T. F. Molinski and J. V. Turner, *Tetrahedron Lett.*, 1984, **25**, 2061.
19 PhLi was the reagent of choice for this reaction. In contrast, use of *n*-BuLi resulted in a poorer yield and conversion (39% yield of **12**, 26% recovery of the starting material **11a**).
20 These products were obtained as diastereomer mixtures (*ca.* 1 : 1), which were used for further cyclization reaction without separation.
21 K. Kamita, C. Watanabe, H. Endang, M. Umar and T. Satake, *Chem. Pharm. Bull.*, 2001, **49**, 551.
22 K.-R. Min, B.-Y. Hwang, H.-S. Lim, B.-S. Kang, G.-J. Oh, J. Le, S.-H. Kang, K.-S. Lee, J.-S. Ro and K. Youngsoo, *Planta Med.*, 1999, **65**, 460.
23 (*a*) Y. Kashiwada, G. Nonaka and I. Nishioka, *Chem. Pharm. Bull.*, 1984, **32**, 3461; (*b*) R. Saijo, G. Nonaka and I. Nishioka, *Phytochemistry*, 1989, **28**, 2443.
24 (*a*) S.-B. Wan and T.-H. Chan, *Tetrahedron*, 2004, **60**, 8207; (*b*) K. K. Khi, Z. A. Kuliev, A. D. Vdovin, M. R. Yagudaev and V. M. Mailikov, *Chem. Nat. Compd.*, 1991, **27**, 681.




 