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# A Regiodivergent Synthesis of Ring A C-Prenylflavones

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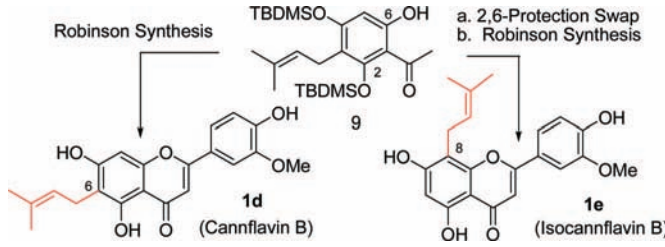
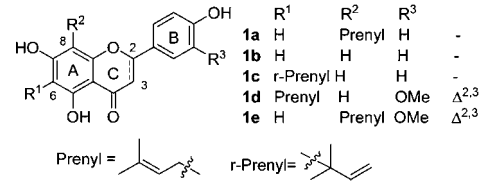
## ABSTRACT




**Capitalizing on the use of orthogonal protecting groups and the development of a modified Robinson flavone synthesis that avoids harsh acidic conditions, a regioselective synthesis of 6- and 8-prenylflavones from the same prenylated disilylated phloracetophenone (9) has been developed, targeting cannflavin B (1d), the COX-inhibiting principle of marijuana, and its unnatural isomer isocannflavin B (1e) as model compounds.**

Over the past few decades, an impressive number of bioactivities have been demonstrated for C-prenylated flavonoids, including binding to several hot targets of current biomedical research such as estrogen receptors (ERs),[1] heat shock proteins (Hsp-90),[2] cyclo-oxygenases (COXs),[3] P-glycoproteins (PgPs),[4] and phosphodiesterases (PDEs).[5] While in most cases it is not clear whether the prenyl group has a specific role for bioactivity, some interesting findings emerged during the study of the estrogenic activity of 8-prenylnaringenin (8PN, Scheme 1, **1a**), a hop and beer constituent.[1] Thus, while the introduction of an 8-prenyl group induces estrogenic activity on the otherwise nonestrogenic flavanone naringenin (**1b**),[1] this operation is detrimental for the estrogenic properties of the isoflavone genistein,[6] and the introduction of a reversed prenyl at C-6 (**1c**) of naringenin leads to a significant affinity for androgen receptors.[7] Furthermore, 8PN is rapidly absorbed after oral administration, in sharp contrast to the generally poor oral bioavailability of flavonoids.[8] Prenylation of the phloroglucinol A

**Scheme 1.** Structure of 8PN (**1a**), Cannflavins A (**1d**), and Related Compounds




| | $R^1$ | $R^2$ | $R^3$ | |
|---|---|---|---|---|
| **1a** | H | Prenyl | H | - |
| **1b** | H | H | H | - |
| **1c** | r-Prenyl | H | H | - |
| **1d** | Prenyl | H | OMe | $\Delta^{2,3}$ |
| **1e** | H | Prenyl | OMe | $\Delta^{2,3}$ |

(1) Milligan, S. R.; Kalita, J.; Heyerick, A.; Rong, H.; De Cooman, L.; De Keukeleire, D. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 2249–2252.
(2) Hadden, M. K.; Galam, L.; Matts, R. L.; Blagg, B. S. J. *J. Nat. Prod.* **2007**, *70*, 2014–2018.
(3) Barret, M. L.; Gordon, D.; Evans, F. J. *Biochem. Pharmacol.* **1985**, *34*, 2019–2024.
(4) Boumendjel, A.; Di Pietro, A.; Dumontet, C.; Barron, D. *Med. Res. Rev.* **2002**, *22*, 512–529.
(5) Shin, H. J.; Kim, H. J.; Kwak, J. H.; Chun, H. O.; Kim, J. H.; Park, H.; Kim, D. H.; Lee, Y. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2313–2316.
(6) Kitaoka, M.; Kadokawa, H.; Sugano, M.; Ichikawa, K.; Taki, M.; Takaishi, S.; Iijma, Y.; Tsutsumi, S.; Boriboon, M.; Akiyama, T. *Planta Med.* **1998**, *64*, 511–515.
(7) Zierau, O.; Morissey, C.; Watson, R. W.; Schwab, P.; Kolba, S.; Metz, P.; Vollmer, G. *Planta Med.* **2003**, *69*, 856–858.

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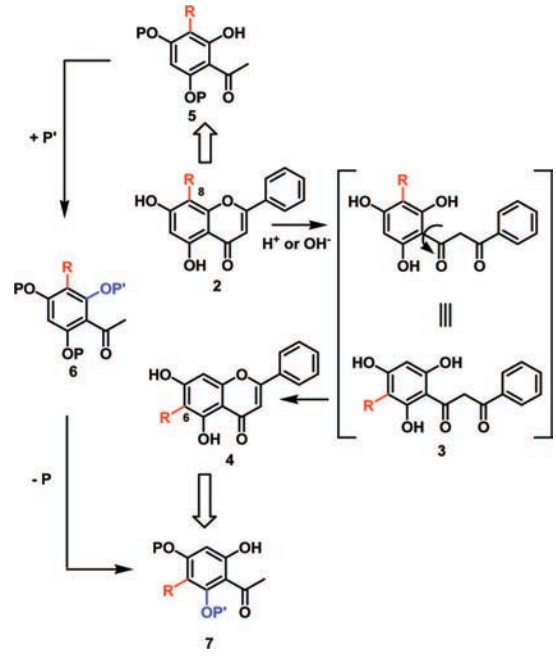
ring can therefore dramatically affect the pharmacodynamic and pharmacokinetic profile of flavanones, justifying a systematic scrutiny of this issue also in flavones, by far the most common type of prenylflavonoids and also their more diverse group in terms of bioactivity.[9]

The shortage of systematic studies on prenylflavones is mainly due to their limited availability by synthesis compared to other classes of prenylated flavonoids. In general, the direct prenylation of flavonoids is difficult to control in terms of chemoselectivity (C- vs O-alkylation), regiochemistry, and number of prenyls introduced, and the issue is better addressed at the stage of their acetophenone precursors. However, the harsh conditions required for the elaboration of acetophenones into flavones (Robinson synthesis)[10] greatly limits the application of this strategy to prenylated derivatives.[11] The development of a straightforward and tunable entry into C-6 and C-8 prenylflavones from a common precursor would therefore represent a significant addition to the field, paving the way to systematic structure−activity studies for this class of compounds. To combine proof-of-concept and relevance, we have investigated the regiodivergent synthesis of cannflavin B (**1d**), the COX-inhibiting principle of marijuana,[3] and its unnatural C-8 regioisomer (isocannflavin B, **1e**) from a common acetophenone precursor. Legal issues aside, cannflavin B is very difficult to obtain by isolation because of its low concentration in marijuana and the occurrence of related phenolics that complicate its purification.[3] Its biomedical potential is therefore still untapped.

To address the problem of the complementary synthesis of C-6 and C-8 prenylflavones, we took inspiration from the Wessely−Moser rearrangement (Scheme 2).[12] This venerable reaction formally interconverts C-8- and C-6-substituted flavones (**2** and **4**, respectively) through a diaroylmethane intermediate that can freely rotate around the C-4a/C-7 axis (**3**).[13] The C-8- and C-6-substituted flavones (**2** and **4**, respectively) are available by Robinson synthesis from their corresponding diprotected, *meta*-substituted phloracetophenone precursors (**5** and **7**, respectively). This operation translates differences in terms of relative orientation of the free hydroxyl and the substituent (*ortho* in **5** and *para* in **7**) at the acetophenone stage into a C-8- or a C-6-flavone substitution pattern. We reasoned that the functional asymmetry of **5** and **7** could be interchanged by a protection swap between the *ortho*-hydroxyls and that this could be achieved through the agency of the orthogonally triprotected intermediate **6** (Scheme 2).

**Scheme 2.** Wessely−Moser Rearrangement of Flavones and Regiodivergent Retrosynthesis of 8- and 6-Substituted Flavones (P and P′ = Orthogonal Protecting Groups)




To put this line of thinking into practice, we had to address two synthetic issues, namely, (a) the design of a 3-prenylphloracetophenone orthogonally protected at the *ortho*-hydroxyls (**6**), and (b) the development of a milder version of the Robinson synthesis, compatible with the presence of acid-labile prenyl groups and the regiodirecting *ortho*-protection of the acetophenone precursors.

Within the various combinations of ether (MEM, MOM), ester (acetate, pivalate), carbamate (BOC, Cbz), and silyl (TES, TBDMS) protecting groups assayed, the 2,4-TBDMS-6-pivaloyl combination (**10**) proved optimal in terms of introduction, stability during the prenylation step, and orthogonality. Thus, the TBDMS group was superior to all

(8) Rad, M.; Huemperl, M.; Schaefer, O.; Schoemaker, R. C.; Schleuniing, W. D.; Cohen, A. F.; Burggraaf, J. *Br. J. Clin. Pharmacol.* **2006**, *62*, 288–296.

(9) For a review, see: Barron, D.; Ibrahim, R. K. *Phytochemistry* **1996**, *43*, 921–982.

(10) There is considerable confusion in the literature regarding the paternity of the preparation of 4*H*-chromones from *o*-hydroxyacetophenones by reaction with an activated carboxylic acid, a transformation referred to as Robinson, Allan−Robinson, Baker−Venkataraman, or Kostanecki−Robinson synthesis. The original Robinson reaction involved a thermal, sodium benzoate catalyzed process, involving *o*-hydroxyacetophenone and aroyl anhydrides: Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, *125*, 2192–2195. A more general two-step protocol based on the base-catalyzed isomerization of *o*-acyloxyacetophenones to *o*-hydroxybenzoylacetophenones followed by cyclization under acidic conditions was later developed and became known as the Baker−Venkataraman synthesis: Baker, W. *J. Chem. Soc.* **1933**, 1381–1389. Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767–1769. While Kostanecki had reported prior to Robinson the formation of flavones by reaction of acetophenones with alkylated salycilic acids in the presence of sodium: von Kostanecki, S.; Rozycki, A. *Ber.* **1901**, *349*, 102–109. For sake of clarity, we refer to the transformation of *o*-hydroxyacetophenones to flavones simply as the "Robinson reaction". For a discussion, see: Finar, I. L. *Organic Chemistry*; Longman: London, 1977; Vol. 2, pp 782−784.

(11) Alternative strategies are the dehydrogenation of prenylflavanones to prenylflavones by treatment with iodine in pyridine (Dong, X.; Fan, Y.; Yu, L.; Hu, Y. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 372–376. ) or the use of robust acid-sensitive, but difficult to remove, protecting groups.

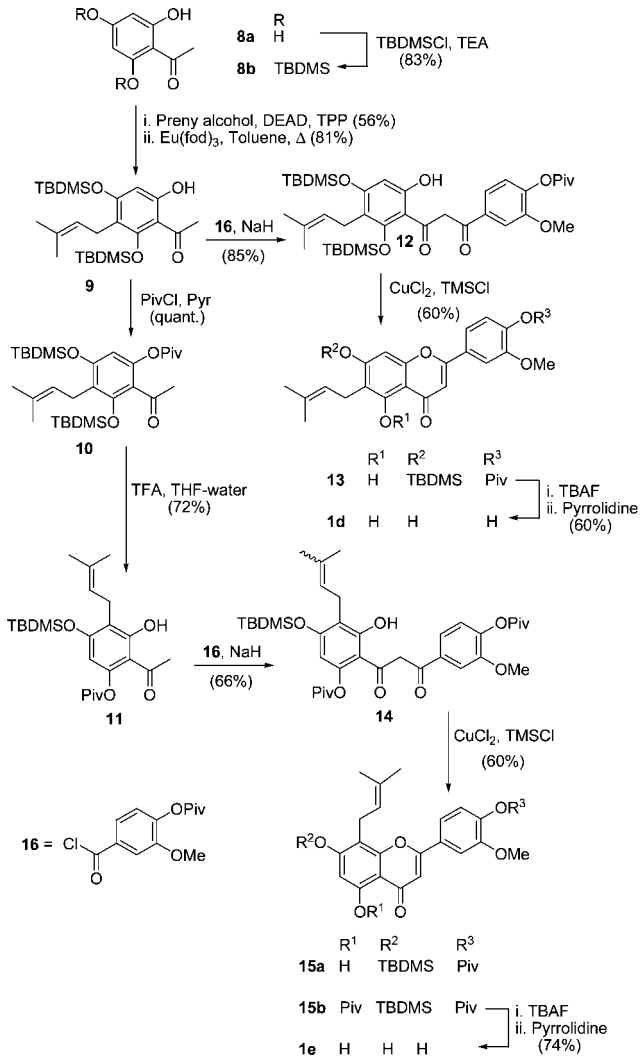
(12) Wessely, F.; Moser, G. H. *Monatsch. Chem.* **1930**, *56*, 97–105.

(13) Flavone numbering.

(14) MOM-Cl has been reported to selectively diprotect phloracetophenone (Bu, X. Y.; Zhao, L. Y.; Li, Y. L. *Synthesis* **1997**, 1246–1248), but, in our hand, this procedure gave a chromatographically difficult to separate 2.5:1 mixture of di- and triprotected derivatives, in analogy with what observed with ester and carbamate protecting groups. An improved procedure has been recently reported: Khupse, R. S.; Erhardt, P. W. *J. Nat. Prod.* **2007**, *70*, 1507–1509.

other groups investigated for the protection of the nonchelated hydroxyls of phloracetophenone (**8a**).[14] Furthermore, unlike the MOM and the pivaloyl groups,[15] it remained unscathed during the conditions [heating in toluene in the presence of $Eu(fod)_3$] required for the tandem Claisen−Cope rearrangement that installed the C-prenyl group from its corresponding O-prenyl derivative,[16] the result of the Mitsunobu alkylation of **8b** (Scheme 3).[17]

**Scheme 3.** Synthesis of Cannflavin B (**1d**) and Isocannflavin B (**1e**)




The key C-prenyl disilylated intermediate **9** was next pivaloylated to **10** and then chemoselectively *ortho*-desilylated by mild acidolysis with TFA in THF/water. Overall, the protection swap between the *ortho*-hydroxyls could be achieved in 72% yield. In this way, a pair of acetophenones (**9** and **11**) complementary in terms of further elaboration to flavones was obtained.

During the harsh acidic conditions required for the conversion of acetophenones to flavones, protection at the *ortho*-hydroxyls is generally lost, even with robust protecting groups like MOM,[18] making the acid-labile prenyl prone to cyclization with the adjacent hydroxyl(s).[19] Furthermore, phenolic protection was also at the basis of the functional asymmetry required by the regiodivergent elaboration of **10** into the target flavones. Given the potential lability of phenolic silyl ether and the pivaloyl group to basic conditions, the C-acylation of **9** and **11** was an additional source of concern. In practice, this step could be achieved without loss of *ortho*-protection by treatment of **9** and **11** with pivaloyl-protected vanilloyl chloride[20] under NaH promotion,[21] affording in excellent yield the diaroylmethanes **12** and **14**. For their dehydration to flavones, we screened a variety of Lewis acids as an alternative to the Brønsted acids currently used for this purpose.[22] The agents investigated proved either unreactive ($CeCl_3 \cdot 7H_2O$), led to massive degradation of the substrate [$BF_3$, $BBr_3$, $Eu(fod)_3$], or gave an equimolecular mixture of 7-TBDMS-4′-pivaloyl cannflavin B (**13**) and isocannflavin B (**15a**) and their corresponding 7-desilyl derivatives ($FeCl_3 \cdot 6H_2O$,[23] $CuCl_2$, scandium and ytterbium triflates). Variable amounts of pyranyl ethers were also formed by cyclization of the prenyl group on the adjacent C-7 hydroxyl.[24] The formation of equimolecular mixtures of 6- and 8-substituted flavones is surprising since, at least under Brønsted acid catalysis, the Wessely−Moser rearrangement is biased toward 6-substituted flavones, and a prevalence of compounds from the cannflavin series was therefore expected.[25]

Taken together, our observations suggest that functional symmetrization by loss of the *ortho*-protecting group (TBDMS for **12**, pivaloyl for **14**) is faster than the intramolecular dehydration of the *o*-hydroxy-1,3-diaroylmethane system.[26] Both **12** and **14** were completely enolized in solution,[27] and

(15) While the thermal instability of the MOM group, especially in the presence of Lewis acids, has been observed previously (Khupse, R. S.; Erhardt, P. W. *J. Nat. Prod.* **2007**, *70*, 1507–1509), that of the pivaloyl group was unexpected and might be related to traces of triphenylphosphine oxide from the Mitsunobu O-prenylation step. Nicolaou, K. C.; Lister, T.; Denton, R. M.; Gelin, C. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7501–7505.

(16) Gester, S.; Metz, P.; Zierau, O.; Vollmer, G. *Tetrahedron* **2001**, *57*, 1015–1018.

(17) Williamson prenylation (prenyl bromide, $K_2CO_3$, acetone) gave a complex mixture of desilyated products.

(18) Urgaonkar, S.; Shaw, J. T. *J. Org. Chem.* **2007**, *72*, 4582–4585.

(19) Wilhelm, H.; Wessjohan, L. A. *Tetrahedron* **2006**, *62*, 6961–6966.

(20) Alkoxy-substituted aroyl chlorides are poor acylating agents in flavone synthesis (Patonay, T.; Molnar, D.; Muranyi, Z. *Bull. Soc. Chim. Fr.* **1995**, *32*, 233–242), and the pivaloyl group was chosen to increase the electrophilicity of the acyl carbon. No reaction took place when pivaloylvanillic acid was reacted with **9** under Steglich conditions (DCC, DMAP).

(21) The reaction takes place with a Baker−Venkataraman oxygen-to-carbon acyl shift, and its course could be followed by TLC (see Supporting Information). The best conditions for the reaction required the treatment with 1 equiv of NaH to produce an *O*-acyl ester, next converted in situ into the C-acylated product by treatment with 2 further equiv of NaH. The direct addition of a large excess of NaH gave a lower yield, while LDA and NaHMDS led to desilylated products.

(22) Due to a decreased basicity, aryl *tert*-butyldimethylsilyl ethers are more stable to Lewis acids than their alkyl analogues: Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.

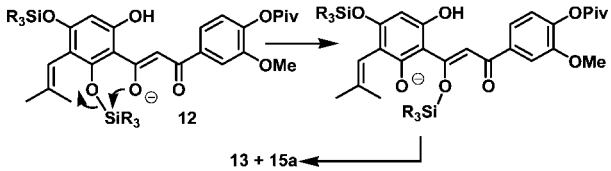
(23) Hard Lewis acids such as $BBr_3$ gave exclusively pyranyl derivatives: Kumar, K. H.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 9531–9535.

(24) Narender, T.; Reddy, K. P. *Tetrahedron Lett.* **2007**, *48*, 7628–7632.

(25) Kazuki, S.; Yoshio, H.; Taro, N. *Heterocycles* **2000**, *53*, 877–886.

(26) $CuCl_2$ has been reported to dehydrate *o*-hydroxy-1,3-diaroylmethanes to flavones under microwave irradiation: Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2005**, *46*, 6315–6317.

**Scheme 4.** Possible Mechanism for the Desilylation of the Diaroylmethane **12** by Lewis Acids (R = *tert*-Butyldimethylsilyl)




it is not unconceivable that the premature functional symmetrization takes place by intramolecular silyl or acyl migration from the phenolic hydroxyl to the proximal (or distal) enol oxygen (see Scheme 4 for silyl migration to the proximal enolic hydroxyl).[28] While deprotection is essentially an irreversible step, cyclodehydration involves a series of equilibria,[27] and we reasoned that removal of water formed in the reaction might be beneficial to prevent, or at least limit, the premature *ortho*-deprotection of **12** and **14** during their elaboration to flavones. Within the Lewis acids assayed, $CuCl_2$ was remarkable since, while leading to symmetrization, it nevertheless left the prenyl and the 7-silyl unaffected in the course of the reaction, and we therefore focused on this reagent to further explore the reaction.

After considerable experimentation with various dehydrating agents, we eventually found that loss of functional asymmetry could be greatly limited for **12** and totally prevented for **14** by the addition of dehydrating agents such as TMS-chloride. Under these conditions, **12** cleanly afforded a reproducible 5:1 mixture of **13** and **15a**, while **14** was regioselectively converted to **15b**.[29] Despite the potential detrimental effect caused by HCl generated from the reaction of TMS-Cl with water, desilylation of the *ortho*-hydroxyl was substantially delayed to the flavone level, while the *ortho*-pivaloyl group remained unscathed also at the flavone level. Global deprotection of **13** and **15b** was then uneventful and afforded cannflavin B (**1d**) and isocannflavin B (**1e**) in overall 31 and 19% yield, respectively, from the prenylated acetophenone **9**.[30]

(27) Nagarathnam, D. Cushman, M. *Tetrahedron* **1991**, *47*, 5071–5076. In general, enolization of 1,3-diaroylmethanes is fast in the presence of a *ortho*-phenolic hydroxyl (see ref 16).

(28) *o*-Hydroxy-1,3-diaroylmethanes exist as an equilibrating mixture of the dicarbonyl form, two enol forms, and one 2-hydroxyflavanone structure, whose composition depends on the aryl substitution pattern: Borbély, J.; Szabó, V.; Sohár, P. *Tetrahedron* **1981**, *37*, 2307–2312. Dehydration of the 2-hydroxyflavanone cyclic tautomer affords flavones: Cunnigham, B. D. M.; Lowe, P. R.; Threadgill, M. D. *J. Chem Soc., Perkin Trans. 2* **1989**, 1275–1283.

In conclusion, we have developed a regiodivergent entry into ring A prenylflavones based on the synthesis of a pair of acetophenones (**9** and **11**) complementary in terms of further elaboration to flavones and on their cyclodehydration by a milder version of the Robinson synthesis. Despite the considerable efforts requested for its completion, the final synthesis is operatively simple and has general application for the preparation of 6- and 8-substituted flavones, circumventing the harsh conditions required for the Robinson synthesis and making it possible to address the issue of prenylation, as well as the introduction of other labile functionalities, at the "easier" phloracetophenone stage.

Flavonoids and polyphenolics have an enormous biomedical and nutritional interest, but their chemistry is still substantially undeveloped and highly dependent on protecting groups. In carbohydrates, the "aliphatic" version of polyphenolics in terms of hydroxy functionalities, protecting groups have acquired a status that goes beyond the simple masking of a specific hydroxyl and encompasses a critical strategic role.[31] Our regiodivergent synthesis of prenylflavonoids demonstrates that these concepts can be successfully applied in polyphenolic chemistry as well.

**Acknowledgment.** This work was supported by Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Roma), and by Università del Piemonte Orientale.

**Supporting Information Available:** Experimental details, spectroscopic characterization, and $^1$H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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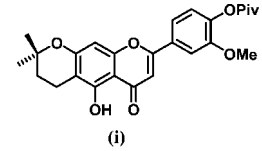
(29) TBDMS-chloride and TES-chloride were less effective, while TMS-triflate gave 4′-pivaloylcyclocannflavin B (i) as the major reaction product. Heterogeneous dehydrating agents (activated molecular sieves) were ineffective, as was trimethylorthoformate or azeotropic removal of water with Dean−Stark distillation. The mechanism by which TMS-chloride postpones desilylation of the *ortho*-hydroxyl to the flavone level might be more complex than a simple water trapping and might involve amplification of the oxyphilicity of the metal catalyst, activation of the "distal" carbonyl of the diaroylmethanes **12** and **14**, or a combination of both.




(i)

(30) For the spectroscopic characterization of cannflavins, see: Choi, Y. H.; Hazekamp, A.; Peltenburg-Looman, A. M. G.; Frédérich, M.; Erkelens, C.; Lefeber, A. W. M.; Verpoorte, R. *Phytochem. Anal.* **2004**, *15*, 345–354.

(31) For a discussion, see: Kocieński, P. J. *Protecting Group*, 3rd ed.; Thieme: Stuttgard, 2003; pp 26−36.