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Microwave-assisted C-3 selective oxidative radical alkylation of flavones†

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Flavones were directly alkylated at the C-3 position in moderate yields using a xanthate-based oxidative radical addition procedure. This methodology is a suitable synthetic tool for the direct substitution of the vinylic and unactivated C–H bond of the C ring of the flavone by an alkyl functionality under neutral conditions.

Flavones are natural products of the benzopyran type (*i.e.* nevadensin **1** and flavone **2**, Fig. 1) and are widely distributed in nature as secondary metabolites in fruits and vegetables.[1] This family of molecules possesses a wide variety of biological activities, including anxiolytic,[2] antiviral,[3] antiprotozoal,[4] anticarcinogenic,[5] antioxidant[6] and antihyperglycemic properties,[7] among others.[1]

In addition to the basic common natural flavonoids that exhibit a C-3 unsubstituted framework, many members of this family are alkylated or oxygenated at this position (Fig. 1). For instance, 3-prenyl derivatives of primuletin (5-hydroxyflavone) **3** and chrysin (5,7-dihydroxyflavone) **4**, can be found in the aerial parts of *Sida cordifolia* (Malvaceae), and both have shown analgesic and anti-inflammatory activities.[8] Furthermore, apigeninyl-(I-3,II-3)-naringenin **5** and related natural products were isolated from the crude extract of the root of *Ormocarpum kirkii* S. Moore (Papilionaceae).[9] These molecules were found to display antiplasmodial activity, a property suspected to contribute to the antimalarial use of *O. kirkii* in Tanzanian traditional medicine.[9]

In medicinal chemistry, transforming or simply modifying natural products, especially those that may be obtained in considerable quantities and with demonstrated pharmacological activity, is of increasing importance in the search for drug leads with improved biological activity. In this context, several synthetic approaches for the construction of the flavone ring system with a wide range of functionalities have been developed over the last decade.[10] In contrast, the direct functionalization of an already prepared or isolated flavonoid has been less studied.[11] Functionalization of a flavone ring system entails special importance because several flavonoids could be extracted in gram scale from their natural sources, and might give rapid access to libraries of diverse flavonoid scaffolds. Toward this goal, various methodologies for the alkylation at C-3 have been described in the literature. A direct alkylation at C-3 could be achieved *via* lithiation with lithium diisopropylamide (LDA) and subsequent trapping of the anion with an appropriate electrophile.[11g–i] In addition to the strongly basic conditions required for this method, its main disadvantage is that flavones containing methoxy groups or other directing substituents might not afford good regioselectivity. Additionally, the introduction of an alkyl substituent at C-3 could also be achieved using a palladium-mediated cross coupling process using 3-haloflavones as starting materials.[11e,l,m] The scope of this latter process is limited by the availability of 3-haloflavones. Thus, a process that avoids the use of strong basic conditions, expensive transition metal complexes, and prefunctionalized starting material would therefore be a

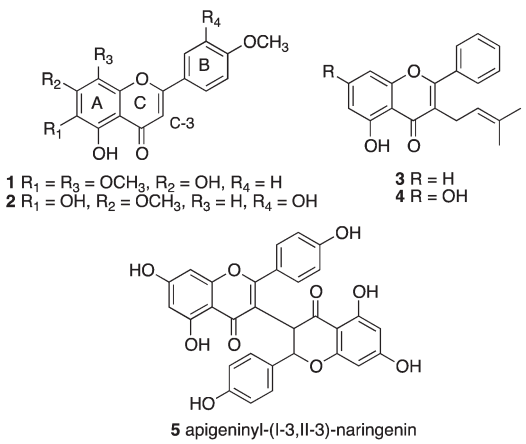

Fig. 1 Leading examples of natural flavonoids.

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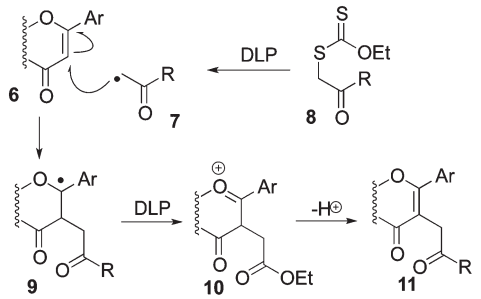


Scheme 1 Proposed mechanism for the oxidative radical addition to flavones.

valuable and straightforward synthetic strategy for preparing flavone derivatives.

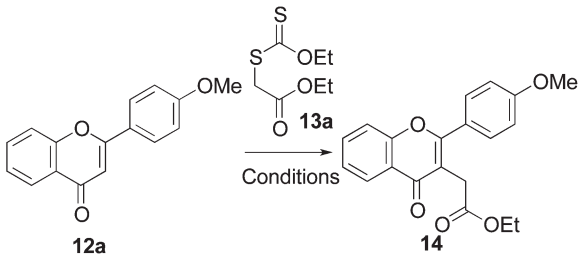
In the search for milder and more versatile reaction conditions and new patterns of reactivity, the use of free radicals has gained importance in synthetic organic chemistry.[12] In particular, xanthate-based radical addition processes developed by Zard and coworkers are powerful tools for constructing C–C bonds under metal-free conditions.[13] Taking all these observations into consideration, we wondered if the flavone ring system (**1**) could be selectively alkylated at C-3 using a xanthate-based radical addition process to obtain the corresponding alkylated flavones (Scheme 1). Preliminary results of our endeavors in this field are presented herein.

The mechanism proposed for the addition process is depicted in Scheme 1. The oxygen-stabilized benzyl radical **9** would be generated upon the addition of the radical **7**, formed from the xanthate **8**, to the flavone **6**. In principle, the radical intermediate **9** would be prone to oxidize to the benzyl oxonium ion **10**, particularly in the presence of a stoichiometric quantity of dilauroyl peroxide (DLP).[14] Deprotonation would furnish the expected alkylated product **11**.

Several flavones were prepared according to a known two-step sequence.[15] We first examined the reaction of the 4′-methoxyflavone **12a**[15] with xanthate **13a** to evaluate the viability and efficiency of the reaction. Relevant observations are reported in Table 1. Heating a 1,2-dichloroethane (DCE) solution of **12a** with 2.0 equivalents of xanthate **13a** and 1.5 equivalents of DLP at reflux temperature for 5 h afforded the desired 3-alkylsubstituted flavone **14** in 39% yield as the only product (found by TLC analysis), with the recovery of a considerable amount of starting flavone **12a** (Table 1, entry 1). Because of the long reaction time, we elected to examine the process under microwave (MW) irradiation conditions. Thus, microwave irradiation (250 W) of a DCE solution of **12a** produced **14** in 41% yield (62% based on the recovered starting flavone **12a**) within 30 min (Table 1, entry 2). In addition, when the reaction was performed without solvent,[16] compound **14** was formed in a similar 39% yield, but with a lower conversion yield. The structure of **14** was confirmed by X-ray crystallography (Fig. 2).

To study the versatility, scope, and the synthetic value of the methodology, we then submitted several flavones to the alkylation process with various xanthates (Table 2), setting optimized conditions as follows: 0.6 mM of flavone in 2 mL of dry DCE, 1.5 eq. of DLP, and 2.0 eq. of xanthate; the mixture was irradiated with microwaves in an open vessel system (Discover,

Table 1 Optimization for the oxidative radical addition to flavones



Entry	Conditions	% Yield **14**	% Conv.[a]
1	DLP/DCE/reflux/5 h	39	58
2	DLP/DCE/MW/reflux/30 min	40	62
3	DLP/solventless/MW/105 °C/30 min	39	50

[a] % Conversion based on recovered starting flavone.

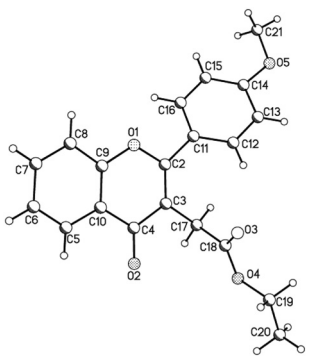
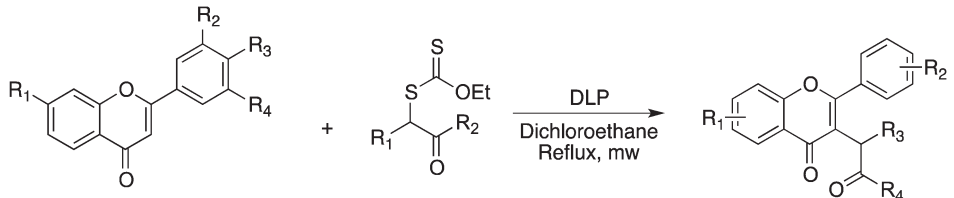


Fig. 2 X-Ray crystal structure of alkylated flavone **14**.

CEM apparatus).[17] The temperature was maintained at 73 °C, by power modulation from 200 to 250 W and with simultaneous cooling of the flask with pressurized air.

By and large, we obtained moderate yields of the 3-alkylsubstituted flavones along with considerable amounts of recovered starting flavones. Remarkably, the substituent at the aromatic B ring had no drastic effect on the yield of the reaction. We also isolated generally good product yields with the ethyl ester-derived xanthate **13a** (Table 2, **15**, **16**, **19**, **29**). The use of benzophenone-derived xanthates **13b** and **13c** afforded slightly lower yields of the alkylated flavones **20–23** and **25–27**, respectively (Table 2). When we subjected the highly oxygenated (A-ring) natural nevadensin **1**[18] to the same alkylating process using the xanthate **13a**, we observed only a complex mixture of products. The failure of this reaction might be due to the abstraction of the hydrogen of the phenols by radicals formed in the medium. It is worth noting that reaction of the dimethylated derivative of **1**[18] with xanthate **13a** under the same conditions provided the expected alkylated product **19** in moderate yield. We observed a similar result when the *p*-Cl–benzophenone xanthate derivative **13b** was reacted with di-MeO-**1** (Table 2, **23**). Furthermore application of the alkylation process to the trimethylated derivative of 5,6,3′-trihydroxy-7,4′-dimethoxyflavone **2**[19] afforded the C-3 alkylated flavonoids **28** and **29** in 51% and 29% yields,

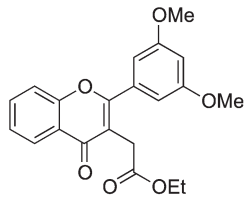
Table 2 Scope of the oxidative radical addition to flavones

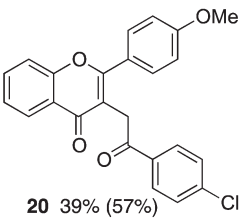


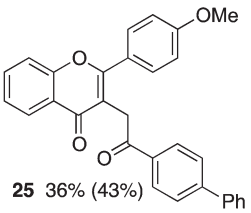
12a R_1 = H, R_3 = OMe, R_2 = R_4 = H
12b R_1 = H, R_3 = H, R_2 = R_4 = OMe
12c R_1 = H, R_2 = R_3 = R_4 = OMe
12d R_1 = OMe, R_3 = OMe, R_2 = R_4 = H

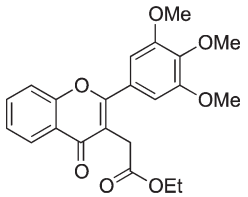
13a R_1 = H, R_2 = OEt
13b R_1 = H, R_2 = *p*-ClC_6H_4
13c R_1 = H, R_2 = *p*-PhC_6H_4
13d R_1 = Me, R_2 = OEt

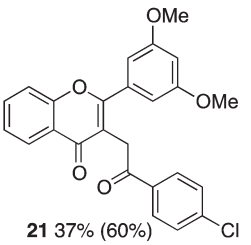
15-29

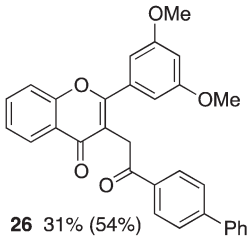

15 45% (73%)

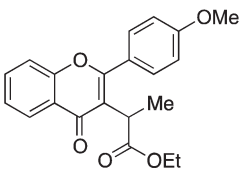

20 39% (57%)

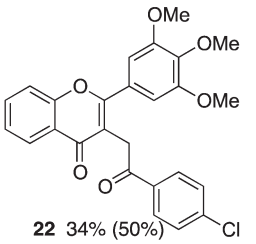

25 36% (43%)

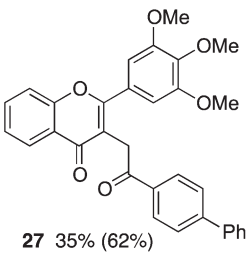

16 42% (52%)

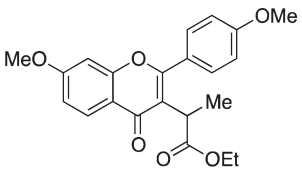

21 37% (60%)

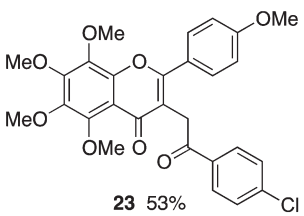

26 31% (54%)

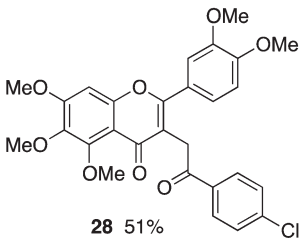

17 19% (23%)

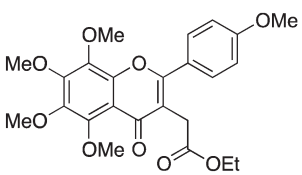

22 34% (50%)

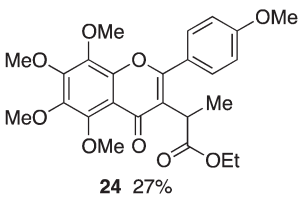

27 35% (62%)

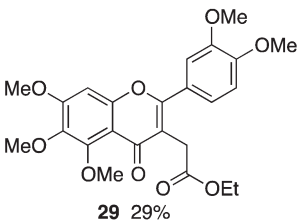

18 50% (88%)


23 53%


28 51%


19 49 % (62%)

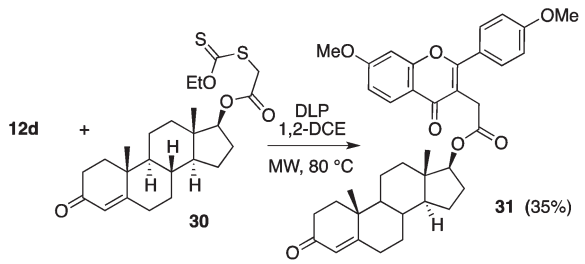

24 27%


29 29%

(%): Yield based on recovered starting material.

respectively. Finally, to further explore the scope of the reaction, a secondary xanthate **13d** was prepared from the corresponding ethyl-2-chloropropionate. Thus, we established that a secondary radical could also be added to the C-3 position of the flavonoid ring system giving **17**, **18** and **24** in moderate yields under the aforementioned conditions (Table 1).

The results in Table 2 convincingly showed that this xanthate-based oxidative radical addition is a suitable synthetic tool for



Scheme 2 Synthesis of the flavone–testosterone conjugated **31**.

the direct substitution of an alkyl functionality at the vinylic and unactivated C–H bonds of the C ring of the flavone, under formally neutral conditions. It is important to mention that in most cases the moderate yields of 3-alkyl flavones did not originate from a lack of selectivity of the radical addition as indicated by the considerable amount of recovered starting material. We then turned our attention to establish that this direct regioselective radical alkylation may be useful to covalently join flavones with other synthetic or natural platforms, giving access to more complex flavone–conjugate scaffolds in the search for enhanced or diverse biological activities. Accordingly, we were pleased to find that the testosterone-derived xanthate **30** (see ESI† for the synthesis) reacted with the flavone **12d** and afforded the flavone–testosterone conjugate **31**, albeit in a modest 35% yield (Scheme 2).

Conclusions

We have developed a convenient synthesis that affords C-3-substituted flavones in moderate yields through a process that involves an intermolecular oxidative radical alkylation. To the best of our knowledge, the synthetic utility of free radicals with flavones has not been explored previously. This direct method offers preparative advantages over the established synthesis of such substituted flavones since it provides a good variety of products and allows the use of mild conditions with great selectivity. Results presented herein could be useful for accessing the synthesis of naturally occurring 3-alkyl flavones (*i.e.*, apigeninyl-(I-3,II-3)-naringenin **5**) and flavone–conjugate scaffolds. It is interesting that the flavone's natural tendency to trap radicals (as the antioxidant molecules they are) has not been applied for organic synthesis.[20]

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Notes and references

1 (*a*) A. K. Verma and R. Pratap, *Nat. Prod. Rep.*, 2010, **27**, 1571–1593; (*b*) O. M. Andersen and K. R. Markham, *Flavonoids: Chemistry, Biochemistry, and Applications*, CRC Press, Boca Raton, FL, 2006; (*c*) S. Martens and A. Mithofer, *Phytochemistry*, 2005, **66**, 2399–2407.
2 M. Marder and A. C. Paladini, *Curr. Top. Med. Chem.*, 2002, **2**, 853.
3 J. A. Manthey, K. Grohmann and N. Guthrie, *Curr. Med. Chem.*, 2001, **8**, 135.
4 A. Fournet and V. Muñoz, *Curr. Top. Med. Chem.*, 2002, **2**, 1215.
5 (*a*) M. Cárdenas, M. Marder, V. C. Blank and L. P. Roguin, *Bioorg. Med. Chem.*, 2006, **14**, 2966, and references therein (*b*) T. Akama, Y. Shida, T. Sugaya, H. Ishida, K. Gomi and M. Kasai, *J. Med. Chem.*, 1996, **39**, 3461.
6 B. Havsteen, *Biochem. Pharmacol.*, 1983, **32**, 1141–1148.
7 J. Shin, K. Kim, M. Kim, J. Jeong and B. Kim, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 869–874.
8 R. K. Sutradhar, A. K. M. M. Rahman, M. U. Ahmad and S. C. Bachar, *Phytochem. Lett.*, 2008, **1**, 179–182.
9 L. Dhooghe, S. Maregesi, I. Mincheva, D. Ferreira, J. P. J. Marais, F. Lemière, A. Matheeussen, P. Cos, L. Maes, A. Vlietinck, S. Apers and L. Pieters, *Phytochemistry*, 2010, **71**, 785–791.
10 (*a*) E. Awuah and A. Capretta, *Org. Lett.*, 2009, **11**, 3210–3213; (*b*) B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi and Z. Yang, *J. Org. Chem.*, 2005, **70**, 6097–6100; (*c*) N. Ahmed, H. Ali and J. Van Lier, *Tetrahedron Lett.*, 2005, **46**, 253–256; (*d*) R. Ramajayam, R. Guiridhar, M. Yadav, E. De Clerq and D. Prajapati, *Med. Chem. Res.*, 2005, **14**, 475–487; (*e*) H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 1765–1768; (*f*) L. W. McGarry and M. Detty, *J. Org. Chem.*, 1990, **55** (14), 4349–4354; (*g*) L. Woods and J. Sapp, *J. Org. Chem.*, 1964, **29**, 3445–3447; (*h*) W. Baker, *J. Chem. Soc.*, 1933, 1381.
11 (*a*) P. Da Re, L. Verlicchi and I Setnikar, *J. Org. Chem.*, 1960, **25**, 1097–1100; (*b*) S. Redy, P. Sreenivas, R. Jayaprakash and G. Krupadanam, *ARKIVOC*, 2009, **XIII**, 55–65; (*c*) K. N. Rao and G. Srimannarayana, *Heterocycles*, 1987, **26** (2), 319–323; (*d*) N. Yao, A. Song, X. Wang, S. Dixon and K. Lam, *J. Comb. Chem.*, 2007, **9**, 668–676; (*e*) K. Dahlén, E. Wallén, M. Grotli and K. Luthman, *J. Org. Chem.*, 2006, **71**, 6863–6871; (*f*) M. Smith, L. Klebanoff, C. Morrow and B. Sandel, *J. Org. Chem.*, 1982, **47**, 1702–1706; (*g*) A. Costa, F. Dean, M. Jones and R. Varma, *J. Chem. Soc., Perkin Trans. 1*, 1985, 799; (*h*) M. Detty and R. McGarry, *J. Org. Chem.*, 1988, **53**, 1203–1207; (*i*) L. W. McGarry and M. Detty, *J. Org. Chem.*, 1990, **55** (14), 4349–4354; (*j*) C. Wang, X. Zheng, W. Meng, H. Li and F. Qing, *Tetrahedron Lett.*, 2005, **46**, 5399–5402; (*k*) W. Adam, E. Gogonas and L. Hadjiarapoglou, *Tetrahedron*, 2003, **59**, 7929–7934; (*l*) Y. Joo, J. Kim, S. Kang, M. Noh, J. Ha, J. Choi, J. Lim, C. Lee and S. Chung, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 413–417; (*m*) M. Pal, R. Dakarapu, K. Parasuraman, V. Subramanian and K. Yeleswarapu, *J. Org. Chem.*, 2005, **70**, 7179–7187.
12 (*a*) C. Ollivier and P. Renaud, *Chem. Rev.*, 2001, **101**, 3415; (*b*) H. Yorimitsu and K. Oshima, in *Radicals in Organic Synthesis*, ed. P. Renaud and M. Sibi, Wiley-VCH, Weinheim, 2001; (*c*) M. P. Sibi and T. R. Rheault, in *Radicals in Organic Synthesis*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, Vol. 1, p. 461.
13 (*a*) B. Quiclet-Sire and S. Z. Zard, *Chem.–Eur. J.*, 2006, **12**, 6002; (*b*) B. Quiclet-Sire and S. Z. Zard, *Top. Curr. Chem.*, 2006, **264**, 201; (*c*) S. Z. Zard, in *Radicals in Organic Synthesis*, ed. P. Renaud and M. Sibi, Wiley VCH, Weinhem, 2001, p. 90; (*d*) S. Z. Zard, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 672; (*e*) B. Quiclet-Sire and S. Z. Zard, *Pure Appl. Chem.*, 1997, **69**, 645; (*f*) S. Z. Zard, *Actual. Chim.*, 1993, **3**, 10.
14 For examples of related oxidative processes using dilauroyl peroxide see: (*a*) T. R. Ibarra-Rivera, R. Gamez-Montano and L. D. Miranda, *Chem. Commun.*, 2007, 3485–3487; (*b*) Y. M. Osornio, R. Cruz-Almanza, V. Jimenez-Montano and L. D. Miranda, *Chem. Commun.*, 2003, 2316–2317; (*c*) F. Gagosz and S. Z. Zard, *Org. Lett.*, 2002, **4**, 4345; (*d*) L. Miranda and S. Z. Zard, *Org. Lett.*, 2002, **4**, 1135–1138. 12 (*e*) T. Kaoudi, B. Quiclet-Sire, S. Seguin and S. Z. Zard, *Angew. Chem., Int. Ed.*, 2000, **39**, 732; (*f*) J. Axon, L. Boiteau, J. Boivin, J. E. Forbes and S. Z. Zard, *Tetrahedron Lett.*, 1994, **35**, 1719; (*g*) A. Liard, B. Quiclet-Sire, R. N. Saicic and S. Z. Zard, *Tetrahedron Lett.*, 1997, **38**, 1759; (*h*) N. Cholleton and S. Z. Zard, *Tetrahedron Lett.*, 1998, **39**, 7295; (*i*) T.-M. Ly, B. Quiclet-Sire, B. Sortais and S. Z. Zard, *Tetrahedron Lett.*, 1999, **40**, 2533.
15 K. H. Kumar and P. T. Perumal, *Tetrahedron*, 2007, **63**, 9531–9535.
16 E. Flórez-López, L. B. Gomez-Pérez and L. D. Miranda, *Tetrahedron Lett.*, 2010, **51**, 6000–6002.
17 Microwave reactions were conducted using a CEM Discover Synthesis™ Unit (CEM Corp., Matthews, NC). http://www.cem.com/page176.html
18 For isolation see: E. Maldonado, E. Hernández and A. Ortega, *Phytochemistry*, 1992, **31**, 1413–1414. For dimethylations process see: H.-W. Chu, H.-T. Wu and Y.-J. Lee, *Tetrahedron*, 2004, **60**, 2647–2655.
19 Isolated from *Salvia herbacea*, see also: A. Bisio, G. Romussi, G. Ciarallo and N. Tommasi, *Pharmazie*, 1997, **52**, 330–331. For trimethylations process see: H.-W. Chu, H.-T. Wu and Y.-J. Lee, *Tetrahedron*, 2004, **60**, 2647–2655.
20 E. T. Oganesyan, Y. A. Maltsev and D. E. Tvorovskii, *Russ. J. Gen. Chem.*, 2001, **71** (6), 939–944.