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Sulfonium salts as prenyl, geranyl, and isolavandulyl transfer agents towards benzoylphloroglucinol derivatives

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Abstract—In search for new methods aiming biomimetic synthesis of polyprenylated acylphloroglucinols (PPAPs), we now report the results of an evaluation of sulfonium salts as prenyl, geranyl, and isolavandulyl transfer agents towards benzoylphloroglucinol derivatives, in neutral conditions. As a result, conditions were found for rather efficient C-prenylation of these compounds. The corresponding trimethyl ether gave the best results, but the reaction was accompanied by a deacylation process. Geranyl transfer was also observed, but in low yield, and, interestingly, an isolavandulyl group could be introduced with an appreciable yield.

A large number of plant natural products present an acylphloroglucinol core substituted by prenyl, geranyl, and lavandulyl groups, some representative examples being depicted in Figure 1.[1,2] Acronylin,[3] from *Acronychia pedunculata*, and grandone, from *Clusia grandiflora*,[4] are examples of mono and triprenylated derivatives, while marupone, from *Moronobea pulchra*,[5] is a case of substitution by a geranyl group. Another category is constituted by lavandulyl substituted compounds such as tovophenone A,[6] from *Tovomita brevistaminea*, or weddellianone B,[7] from *Clusia weddelliana*.

Such a substitution pattern offers the possibility to generate a large number of structures. This number is further increased by the ability of formation of cyclized derivatives, possessing a strained bicyclo[3.3.1]nonane core such as, *inter alia*, xanthochymol. Our interest in this field came from the observation[8] that this last mole-

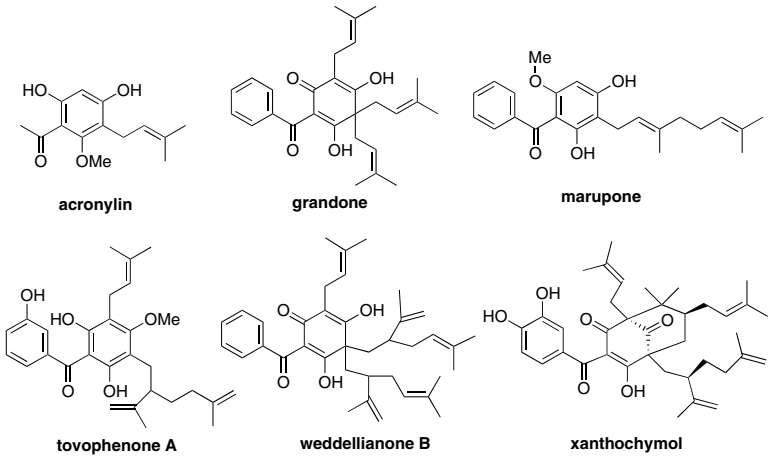

Figure 1.

Keywords: Benzoylphloroglucinol; Sulfonium salts; Biomimetic synthesis; Prenyl transfer; Friedel–Crafts alkylation.
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cule was nearly as active, in vitro, as paclitaxel in a tubulin disassembly inhibition test, and from our recent results concerning isolation of analogs from *Garcinia* species.[9a] These results and considerations encouraged us to engage synthetic studies[9b] towards polyprenylated acylphloroglucinols (PPAPs),[1a] a large family of bioactive natural products.

Prenyl transfer, with dimethylallylpyrophosphate, to the acylphloroglucinol core structure is a key step in the biosynthesis of PPAPs.[1a] As a part of a programme directed towards a biomimetic synthesis of these compounds, we searched smooth conditions for the introduction of prenyl units onto acylphloroglucinols. Thus, prenylation of the phloroglucinol nucleus, before acylation, was not examined, according to biosynthetic considerations. However, this approach has already been reported in the case of a geranylated compound.[10]

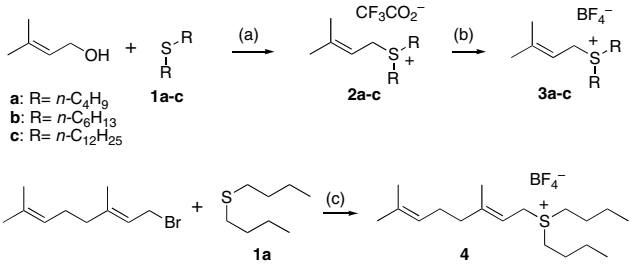
It should be noted that C-prenylation and -geranylation of non-acylated phloroglucinol have been achieved, with the corresponding diisopropylphosphates, but in the presence of one equivalent of BF_3 etherate, and using an excess of the triphenol trimethyl ether.[11] Zeolite catalyzed prenylation of a more oxygenated nucleus with isoprene was also described.[12] Neither *ortho*-lithiation nor lithium–halogen exchange, starting from phloroglucinol ethers derivatives, followed by prenylation and acylation, has been taken into account here.[10,13]

C-Prenylation of acylphloroglucinols has also been already realized with prenyl bromide in basic conditions,[14] with 2-methyl-3-buten-2-ol in the presence of BF_3 etherate[15] or via Claisen rearrangement, starting from the α,α-dimethylallyl phenol ethers.[16]

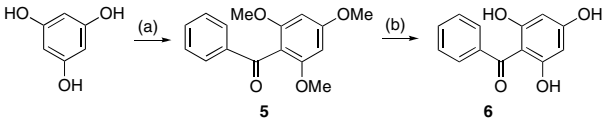
In this Letter, we report results of a study concerning prenyl transfer to benzoylphloroglucinol derivatives, in neutral conditions, with sulfonium salts as reagents. These last compounds were indeed previously reported to be good alkylating agents, in particular prenyl transfer agents, towards enolates (specially for C-alkylation of β-dicarbonyl compounds),[17] and even non activated double bonds.[18]

A series of prenyl sulfonium salts were first prepared according to a procedure described by Julia et al.[19] For this purpose, long alkyl chain sulfides **1a**–**c** (Scheme 1) were chosen in order to obtain sulfonium salts soluble in apolar organic solvents.[20] Thus treatment of prenol with sulfides **1a**–**c** in dichloromethane in the presence of an excess of trifluoroacetic acid, followed by anion exchange, resulted in the formation of sulfonium tetrafluoroborate salts **3a**–**c** in excellent yield. This last procedure was not convenient for the synthesis of geranyl derivatives, which were difficult to purify due to the formation of secondary products. For this reason, salt **4** was obtained from the $AgBF_4$ treatment of geranyl bromide in dichloromethane and recovered as a pure product, in quantitative yield, after simple filtration over Celite.

Benzoylphloroglucinol **6** and its trimethyl ether **5** were then prepared according to Scheme 2.[21]



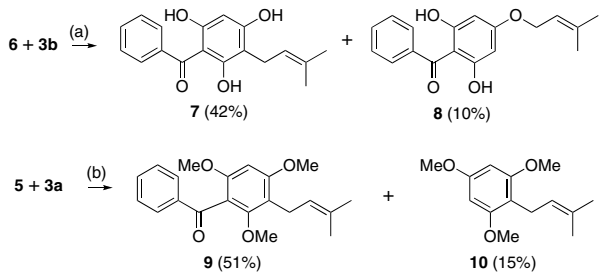
Scheme 1. Reagents and conditions: (a) Prenol (1.5 equiv), CF_3CO_2H (4 equiv), CH_2Cl_2, 20 °C, 20 h; (b) HBF_4 (34% in H_2O), MeOH, 20 °C, 1 h, salts **3a**–**b**: quantitative overall yield from **1a**–**b**, salt **3c**: 88% overall yield from **1c**; (c) $AgBF_4$ (1 equiv), CH_2Cl_2, rt, 2 h, quantitative yield.



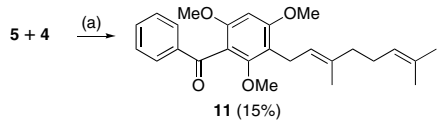
Scheme 2. Reagents and conditions: (a) Ref. 21, two steps, 58%; (b) BBr_3 (5 equiv), CH_2Cl_2, −78 °C, then rt 66 h, 80%.

We first studied prenyl transfer to benzoylphloroglucinol **6** from sulfonium salt **3b** at ambient temperature (Scheme 3). Diisopropylethylamine was used to trap the tetrafluoroboric acid formed in the reaction.[18a] Optimum conditions were determined by a ^1H NMR study, performing the reaction in $CDCl_3$, due to difficult monitoring by TLC (phenolic compounds). This allowed us to observe the total consumption of sulfonium salt **3b**, along with the formation of sulfide **1b**, in 7 h. Extraction, followed by silica gel chromatography using heptane/AcOEt (70/30), led to the isolation of C-prenylated phloroglucinol derivative **7** in 42% yield along with O-alkylated derivative **8** in 10% yield. Use of an excess of sulfonium salt did not improve the yield, giving polyprenylated secondary products.

In order to make TLC analysis and purification easier, and to also evaluate the role of the phenolic hydroxy groups, benzoylphloroglucinol protected as its trimethyl ether **5** was used. Prenylation was undertaken with salt **3a** and we were pleased to observe that the reaction proceeded, but at higher temperature. Optimum conditions were found using an apolar medium.[20] Thus, use of toluene, at 100 °C for 16 h, resulted in formation of the prenyl-



Scheme 3. Reagents and conditions: (a) **3b** (1 equiv), Hünig's base (1.1 equiv), $CHCl_3$, rt, 7 h; (b) **3a** (2.5 equiv), Hünig's base (5 equiv), toluene, 100 °C, 16 h.



Scheme 4. Reagents and conditions: (a) **4** (2.5 equiv), Hünig's base (5 equiv.), toluene, 80 °C, 16 h.

ated adduct **9** in 51% yield, in a smooth uncatalyzed Friedel–Crafts alkylation reaction. Due to some decomposition (probable formation of isoprene), use of an excess of sulfonium salt was necessary in this case. The debenzoylated derivative was also isolated in 15% yield.[22]

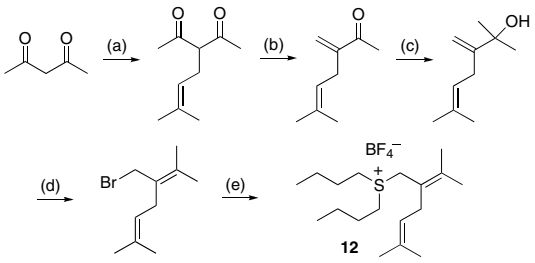
Introduction of a geranyl group, using sulfonium salt **4**, turned to be more difficult, but a marupone analog **11** has been obtained in 15% yield from **5** (Scheme 4).

It should be mentioned that this method could not be used for the transfer of a group that is not of allylic nature, such as a lavandulyl.[23]

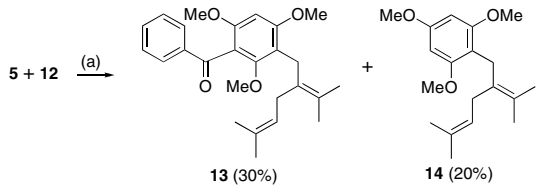
Finally we prepared an isolavandulyl sulfonium derivative from the corresponding bromo compound, according to Scheme 5. The process, for the synthesis of the allylic bromide, consists essentially in an adaptation of known methods.[24,25]

Treatment of benzoylphloroglucinol derivative **5** with an excess of the new sulfonium salt **12** (Scheme 6), in the conditions used previously, afforded the desired substituted derivative **13** in 30% yield, accompanied again by deacylation product **14** in 20% yield.

This last result represents the first example of the introduction of an isolavandulyl framework onto a phloroglucinol derivative.



Scheme 5. Reagents and conditions: (a) Prenyl bromide, EtONa, 0 °C overnight, 96% yield; (b) HCHO (37% in H_2O), K_2CO_3, H_2O, 71% yield; (c) MeLi, Et_2O, 70% yield; (d) PBr_3 (0.5 equiv), pyridine (0.1 equiv), Et_2O, 75% yield; (e) **1a** (1 equiv), $AgBF_4$, CH_2Cl_2, quantitative yield.



Scheme 6. Reagents and conditions: (a) **12** (2.5 equiv), Hünig's base (5 equiv), toluene, 80 °C, 16 h.

In conclusion, we have shown that the sulfonium salts can be usefull derivatives for the introduction of prenyl, geranyl, and isolavandulyl groups onto benzoylphloroglucinol derivatives. The reaction occurs in nearly neutral conditions, unlike other methods, and avoids a multi-step sequence, as for Claisen rearrangement. Moreover, the reagents can be considered as synthetic equivalents for pyrophosphates operating during the biosynthetic process,[1a] when the unprotected triphenol is used. The method is particularly convenient for ether derivatives of the phloroglucinol nucleus. The use of this approach, as well as its evaluation by comparison with other conditions and electrophiles, is in progress with the objective of biomimetic natural products synthesis in these series.

References and notes

1. (a) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963–3986; (b) Singh, I. P.; Bharate, S. B. *Nat. Prod. Rep.* **2006**, *23*, 558–591.
2. (a) Cuesta-Rubio, O.; Piccinelli, A. L.; Rastrelli, L. In *Studies in Natural Product Chemistry (Bioactive Natural Products, Part L)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2005; Vol. 32, pp 671–720; (b) Baggett, S.; Mazzola, E. P.; Kennelly, E. J. In *Studies in Natural Product Chemistry (Bioactive Natural Products, Part L)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2005; Vol. 32, pp 721–771.
3. Kumar, V.; Karunaratne, V.; Meegalle, M. R.; Sanath, K. *Phytochemistry* **1989**, *28*, 1278–1279.
4. de Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427–6430.
5. Dias, J. D. P.; Gottlieb, O. R.; Mesquita, A. A. L. *Phytochemistry* **1974**, *13*, 1953–1955.
6. Seo, E.-K.; Wall, M. E.; Wani, M. C.; Navarro, H.; Mukherjee, R.; Farnsworth, N. R.; Kinghorn, A. D. *Phytochemistry* **1999**, *52*, 669–674.
7. Porto, A. L. M.; Machado, S. M. F.; de Oliveira, C. M. A.; Bittrich, V.; Amaral, M. do C. E.; Marsaioli, A. J. *Phytochemistry* **2000**, *55*, 755–768.
8. Roux, D.; Hadi, H. A.; Thoret, S.; Guénard, D.; Thoison, O.; Païs, M.; Sévenet, T. *J. Nat. Prod.* **2000**, *63*, 1070–1076.
9. (a) Hamed, W.; Brajeul, S.; Mahuteau-Betzer, F.; Thoison, O.; Mons, S.; Delpech, B.; Hung, N. V.; Sevenet, T.; Marazano, C. *J. Nat. Prod.* **2006**, *69*, 774–777; (b) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287–289.
10. Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* **1985**, *26*, 123–126.
11. Araki, S.; Manabe, S.; Butsugan, Y. *Chem. Lett.* **1982**, 797–800.
12. Bigi, F.; Carloni, S.; Maggi, R.; Muchetti, C.; Rastrelli, M.; Sartori, G. *Synthesis* **1998**, 301–304.
13. See, for example: (a) Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. *Tetrahedron Lett.* **2002**, *43*, 291–293; (b) Takaoka, S.; Nakade, K.; Fukuyama, Y. *Tetrahedron Lett.* **2002**, *43*, 6919–6923.
14. see, for example: (a) Riedl, W. *Chem. Ber.* **1952**, *85*, 692–710; (b) Meikle, T.; Stevens, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1303–1312; For prenylation in presence of a strongly basic ion-exchange resin, see: (c) Collins, M.; Laws, D. R. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2013–2015.

15. Cann, M. R.; Davis, A.-M.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1413–1421.
16. (a) Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1971**, *24*, 2355–2363; (b) Tisdale, E. J.; Vong, B. G.; Li, H.; Kim, S. H.; Chowdhury, C.; Theodorakis, E. A. *Tetrahedron* **2003**, *59*, 6873–6887; (c) Nicolaou, K. C.; Xu, H.; Wartmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 756–761.
17. (a) Garst, M. E.; Mc Bride, B. J. *J. Org. Chem.* **1983**, *48*, 1362–1364; (b) Badet, B.; Julia, M.; Lefebvre, C. *Bull. Soc. Chim. Fr.* **1984**, *II*, 431–434; (c) Umemura, K.; Matsuyama, H.; Watanabe, N.; Kobayashi, M.; Kamigata, N. J. *J. Org. Chem.* **1989**, *54*, 2374–2383.
18. (a) Badet, B.; Julia, M.; Marazano, C. *Tetrahedron Lett.* **1985**, *26*, 2007–2010; (b) Julia, M.; Marazano, C. *Tetrahedron* **1985**, *41*, 3717–3724.
19. Badet, B.; Julia, M. *Tetrahedron Lett.* **1979**, *20*, 1101–1104.
20. The alkylating power of sulfonium salts has been shown to be particularly enhanced in apolar medium (see, in particular, Ref. 18b.
21. Pathak, V. P.; Khanna, R. N. *Indian J. Chem.* **1982**, *21B*, 253–254.
22. This alkylation–deacylation process has few precedents in the literature, see: Roth, B.; Aig, E. *J. Med. Chem.* **1987**, *30*, 1998–2004; For related deacylation processes in strong acidic medium see: (a) Keumi, T.; Morita, T.; Inui, Y.; Teshima, N.; Kitajima, H. *Synthesis* **1985**, 979–980; (b) Al-Ka'bi, J.; Farooqi, J. A.; Gore, P. H.; Nassar, A. M. G.; Saad, E. F.; Short, E. L.; Waters, D. N. *J. Chem. Soc., Perkin Trans. 2* **1988**, 943–949.
23. Noteworthy is the observation that the biogenetic origin of a related lavandulyl substituent in *Sophora flavescens* natural products was found to be the result of a prenyl transfer on a prenyl group and not a direct lavandulyl group transfer: Zhao, P.; Inoue, K.; Kouno, I.; Yamamoto, H. *Plant Physiol.* **2003**, *133*, 1306–1313.
24. Fleming, I.; Lee, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2701–2709.
25. Maurin, R.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1972**, 2356–2365.