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A flexible strategy for the divergent modification of pleuromutilin

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The complex antibacterial natural product, pleuromutilin, can be directly modified by the radical addition reaction of various xanthates to the unactivated terminal olefin present on C-12.

The chemical modification of biologically active natural products is essential for determining their structure–activity profile and for improving their potency. The complexity of a lead structure often imposes severe limitations on the type of transformations that can be accomplished. Pleuromutilin, a naturally occuring antibacterial isolated from various basidomycete microorganisms (*e.g. Pleurotus mutilus* and *Pleurotus passeckerianus*),[1] is a case in point. Most of the modifications have concerned the ester side-chain on C-14 and have led to two more potent drugs Tiamulin and Valnemulin, now in veterinary use (Fig. 1).[2] On a structure of this complexity, it is not easy to manipulate the unactivated and relatively hindered olefin on C-12 without extensive protection of the remaining functional groups. We have now found that the radical chain xanthate transfer process[3] is of sufficient mildness to allow the direct creation of new C–C bonds on the olefin in Pleuromutilin without the need for any prior protection.

Heating Pleuromutilin with 3 equivalents of nitrile containing xanthate **1a** in refluxing 1,2-dichloroethane in the presence of a small amount of lauroyl peroxide (*ca.* 40 mol%) gave the addition product **2a** in 80% yield (Scheme 1). We were relieved to find that no complication arose from the glycolate ester portion which contains easily abstractable hydrogens (abstraction of a hydrogen from the methylene group gives a captodative radical).

Under similar conditions, xanthate **1b** proved less efficient since the yield of addition product **2b** was only 35%. Xanthates **1c**, **1d**, and **1e** however, all of which contain a ketone group, added smoothly to give the corresponding adducts **2c**–**e** in 60, 70, and 55% yield, respectively. The possibility of introducing a trifluoromethyl ketone as in the case of **2d** is worth underlining.[4] Such ketones readily and reversibly form hydrates and these are mimics for the tetrahedral intermediates involved in the hydrolysis of esters and amides. They therefore tend to bind well with various types of hydrolytic enzymes.[5] In the case of **2e**, the aromatic group represents in contrast a hydrophobic unit that could significantly modify the lipophilicity of the native pleuromutilin.

The xanthate group in these various adducts represents a further point for the introduction of diversity. There is, however, a poor control of the stereochemisty of the carbon bearing the xanthate and, in order to simplify characterisation, we performed a reductive elimination using tributylstannane or a stoichiometric amount of lauroyl peroxide in 2-propanol.[6] The latter reagent system is better suited for biological testing since no heavy metals are involved. The relatively low yield in the reduction of **2e** is due in part to ring closure of the intermediate radical onto the aromatic ring.[7]

The addition of a benzothiazole group as in **2f** (Scheme 2), albeit inefficient (10 or 50% based on recovered starting material), highlights the possibility of directly incorporating heteroaromatic moieties. More interestingly, the direct and efficient introduction of an activated carboxylic function under the guise of an *N*-acyloxazolidinone, as in **3g**, provides an opportunity for the expedient creation of large libraries of amides and esters since numerous amines and alcohols are commercially available. This is examplified by the synthesis of amides **4a** and **4b**. The glycolate ester on C-14 is not affected in these transformations.†

The above derivatives represent only a tiny sample of the variety of functionality that can be introduced by this strategy, and none is easily accessible by conventional routes. Given the compatibility of radical reactions with many commonly encountered functional groups, this approach represents a new and powerful strategy for the modification of complex, biologically active compounds, with minimal need for protection steps. Moreover, even though only a few natural compounds contain a terminal olefin amenable to this type of functionalisation, it is possible, by a simple allylation or vinylation reaction, to

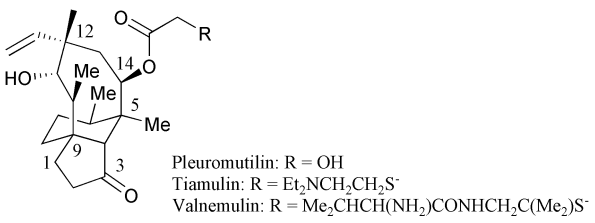
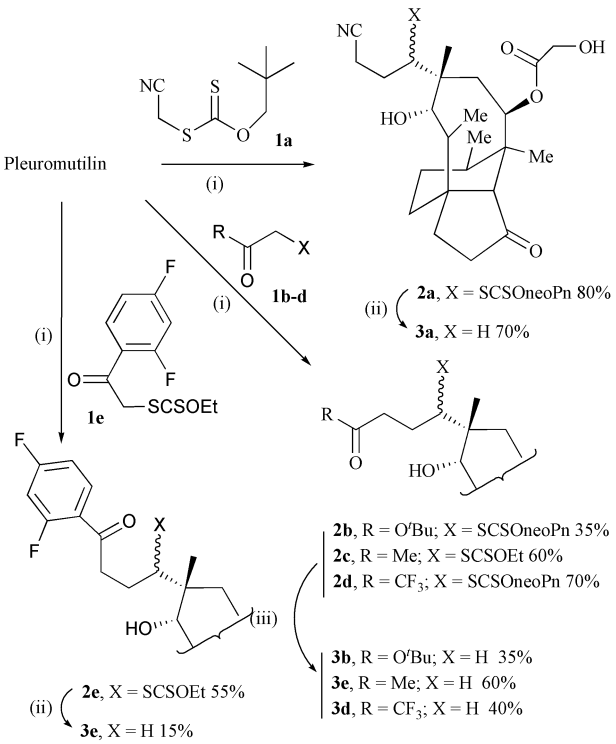


Fig. 1 Pleuromutilin and congeners.



Scheme 1 Radical addition of xanthates to pleuromutilin.

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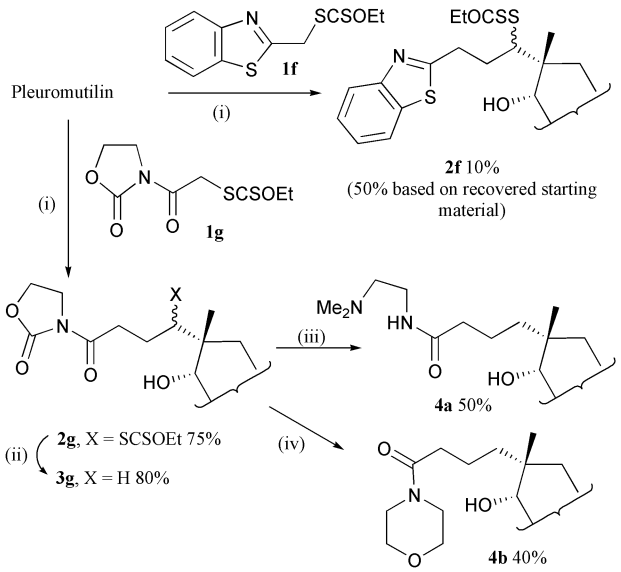

Scheme 2 Radical addition and amide formation.

introduce such an olefin and therefore expand considerably the scope of this technology.

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Notes and references

† *Typical experimental procedure*: compound **1g**: At −10 °C and under nitrogen, a 1.5 M solution of *n*-BuLi in hexane (11.5 ml; 1 eq.) was added dropwise to a stirred solution of oxazolidin-2-one (1.5 g; 17 mmol) in dry THF (35 ml). Chloroacetyl chloride (1.5 ml; 1.1 eq.) was then added dropwise. After 15 min of stirring, the reaction mixture was poured into a mixture of a saturated solution of NH_4Cl and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give 1.8 g (65%) of 3-(2-chloroacetyl)oxazolidin-2-one as a white solid, which was used directly in the next step; δ_H (400 MHz; $CDCl_3$) 4.69 (2H, s), 4.49 (2H, t, *J* 8 Hz), 4.05 (2H, t, *J* 8 Hz); δ_C (100 MHz; $CDCl_3$) 166.1; 153.4, 63.0, 43.3, 42.6; ν_{max} (CCl_4)/cm^{-1} 2923, 1796, 1727, 1711, 1386, 1363, 1343 1255, 1172, 1106, 1045; MS(CI): $[MNH_4]^+$ *m*/*z* 181 and 183. At r.t. and under nitrogen, 1.9 g (1.1 eq.) of KSC(S)OEt were slowly added to a stirred solution containing 1.75 g (10.7 mmol) of 3-(2-chloroacetyl)oxazolidin-2-one in 5 ml of acetone. After a few minutes of stirring, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 2.9 g of a yellow solid. Recrystallisation from heptane–EtOAc afforded 2.4 g (90%) of compound **1g** as colourless needles (mp 96 °C); δ_H (400 MHz; $CDCl_3$) 4.65 (2H, q, *J* 7 Hz), 4.58 (2H, s), 4.49 (2H, t, *J* 8 Hz), 4.08 (2H, t, *J* 8 Hz), 1.43 (3H, t, *J* 7 Hz); δ_C (100 MHz; $CDCl_3$) 212.9, 166.9, 153.6, 70.9, 62.6, 42.8, 39.6, 13.8; ν_{max} (CCl_4)/cm^{-1} 2990, 2923, 1794, 1716, 1480, 1384, 1227, 1113, 1054, 1011; MS(CI): $[MH]^+$ *m*/*z* 250, $[MNH_4]^+$ 267 (Found (%): C, 38.3; H, 4.5. $C_8H_{11}NO_4S_2$ requires (%): C, 38.5; H, 4.5).

Compound **3g**: lauroyl peroxide (60 mg; 0.1 eq.) was added to a refluxing solution of xanthate **1g** (1.8 g; 7 mmol) and (+)-pleuromutiline (0.54 g; 1.4 mmol) in 2 ml of 1,2-dichloroethane under nitrogen. Further portions of lauroyl peroxide (30 mg; 0.05 eq.) were added every 90 min until completion of the reaction, which took about 10 h. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel to give **2g** (0.67 g; *ca.* 75%; mixture of epimers) as a colourless oil. This oil was dissolved in propan-2-ol (20 ml) and the resulting solution refluxed under nitrogen. After a few minutes, lauroyl peroxide (84 mg; 0.2 eq.) was added. Further portions of peroxide (42 mg; 0.1 eq.) were then added every 90 min until completion of the reaction, which took about 17 h of heating. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel to give compound **3g** as a white foam (0.43 g; 80%); δ_H (400 MHz; $CDCl_3$) 5.73 (1H, d, *J* 8 Hz), 4.5–4.4 (2H, m), 4.2–3.9 (4H, m), 3.40 (1H, d, *J* 4.5 Hz), 3.1–2.8 (3H, m), 2.5–2.0 (4H, m), 1.9–0.8 (14H, m), 1.40 (3H, s), 1.00 (3H, s), 0.97 (3H, d, *J* 7 Hz), 0.68 (3H, d, *J* 7 Hz); δ_C (100 MHz; $CDCl_3$) 217.3, 174.1, 172.5, 153.7, 76.5, 69.5, 62.2, 61.5, 58.6, 45.6, 42.7, 41.8, 41.4, 40.8, 36.7, 35.6, 34.6, 34.5, 30.3, 27.7, 26.90, 26.85, 25.0, 19.3, 16.5, 14.9, 11.3; ν_{max} (CCl_4)/cm^{-1} 3540, 2937, 1791, 1737, 1701, 1462, 1384, 1281, 1225, 1152, 1098; MS(CI): $[MH - HOCH_2COOH - H_2O]^+$ *m*/*z* 414, $[MNH_4 - HOCH_2COOH]^+$ 449, $[MNH_4 - H_2O]^+$ 507, $[MNH_4]^+$ 525 (Found (%): C, 63.8; H, 8.2. $C_{27}H_{41}NO_8$ requires (%): C, 63.9; H, 8.1).

Compound **4a**: compound **3g** (60 mg; 0.12 mmol) was dissolved in 2 ml of a 1:1 mixture of *N*,*N*-dimethylethylene diamine and acetonitrile. After stirring at room temperature under nitrogen for 2 h, the solvent was removed under reduced pressure and the residue dissolved in EtOAc and extracted with 1 M aqueous HCl. The aqueous phase was made basic using solid $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel to give 30 mg (50%) of compound **4a** as a white foam; δ_H (400 MHz; $CDCl_3$) 6.83 (1H, t, *J* 5 Hz), 5.71 (1H, d, *J* 7.5 Hz), 4.11 (1H, d, *J* 17 Hz), 3.99 (1H, d, *J* 17 Hz), 3.52 (1H, m), 3.34 (1H, d, *J* 6 Hz), 3.17 (1H, m), 2.6–0.9 (23H, m), 2.26 (6H, s), 1.37 (3H, s), 0.95 (3H, s), 0.94 (3H, m), 0.67 (3H, d, *J* 6.5 Hz); δ_C (100 MHz; $CDCl_3$) 217.3, 174.6, 172.9, 76.3, 69.1, 61.1, 59.0, 58.8, 45.5, 45.3, 41.7, 41.0, 40.9, 37.8, 36.7, 36.6, 34.7, 34.5, 30.4, 28.0, 26.94, 26.90, 25.1, 21.7, 16.4, 14.8, 11.5; ν_{max} (CCl_4)/cm^{-1} 3406, 2930, 1740, 1682, 1656, 1510, 1461, 1376, 1204, 1105; MS(CI): $[MH - HOCH_2COOH]^+$ *m*/*z* 433, $[MH]^+$ = 509.

1 F. Kavanagh, A. Hervey and W. J. Robbins, *Proc. Natl. Acad. Sci. USA*, 1951, **37**, 570; F. Kavanagh, A. Hervey and W. J. Robbins, *Proc. Natl. Acad. Sci. USA*, 1952, **38**, 550; D. E. Cane, *Tetrahedron*, 1980, **36**, 1109; M. Dobler and B. G. Dürr, *Cryst. Struct. Commun.*, 1975, **4**, 259.
2 (*a*) E. Hunt, *Drugs Fut.*, 2000, **25**, 1163; (*b*) H. Berner, H. Vyplel and G. Schultz, *Tetrahedron*, 1987, **43**, 765.
3 For reviews, see: S. Z. Zard, in *Radicals in Organic Synthesis*, ed. P. Renaud and M. Sibi, Wiley YCH, Weinheim, 2001, pp. 90–108; S. Z. Zard, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 672; B. Quiclet-Sire and S. Z. Zard, *Phosphorus, Sulfur Silicon*, 1999, **153–154**, 137.
4 M.-P. Denieul, B. Quiclet-Sire and S. Z. Zard, *Chem. Commun.*, 1996, 2511.
5 J.-P. Bégué and D. Bonnet-Delpon, *Tetrahedron*, 1991, **47**, 3207; M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555; P. Lin and J. Jiang, *Tetrahedron*, 2000, **56**, 3635.
6 A. Liard, B. Quiclet-Sire and S. Z. Zard, *Tetrahedron Lett.*, 1996, **37**, 5877.
7 A. Liard, B. Quiclet-Sire, R. N. Saicic and S. Z. Zard, *Tetrahedron Lett.*, 1997, **38**, 1759.