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IMPROVED PREPARATION OF ANGELATE ESTERS

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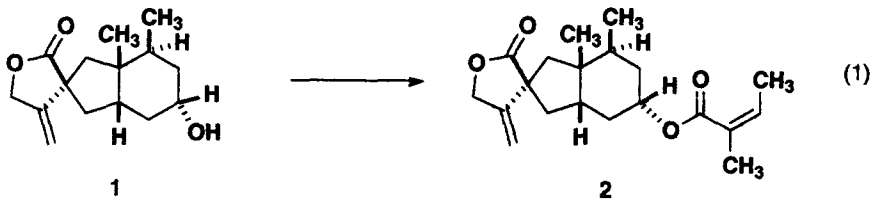
Key words: Esterification, angelate esters, natural products.

Abstract: A new procedure has been developed for the efficient preparation of angelate esters from alcohols. The alcohol is treated in dry toluene at 70-80 °C for 19-36 h with a mixed anhydride prepared from angelic acid and 2,4,6-trichlorobenzoyl chloride. In the absence of base, *no* tiglate ester is produced.

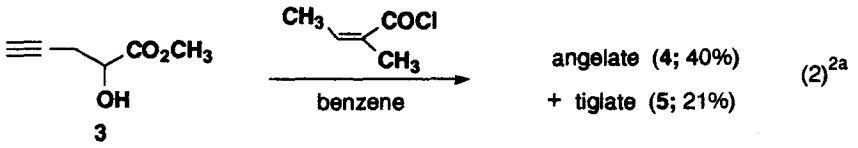
We recently required an efficient esterification procedure for the preparation of the angelate ester homogynolide-A (**2**) from the corresponding alcohol (**1**, eq 1).[1] In that angelates are common



1 **2** (1)

in nature, it was particularly surprising to discover that a methodological lacuna existed for this seemingly straightforward type of conversion.

To effect this esterification most frequently the alcohol has been treated with angeloyl chloride (e.g., eq 2).[2] This procedure, however, usually affords the desired angelate in only poor to modest



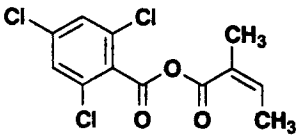
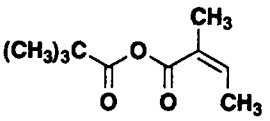
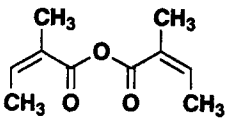
3 (2)[2a]

yield, often together with the corresponding tiglate (which can be the exclusive product). In the presence of pyridine, the tiglate is formed uniquely.[2b,3] Similar results have been obtained with angelic acid in the presence of dicyclohexylcarbodiimide, with or without catalysis.[2c,4,5] The use of the sodium or lithium alkoxide with angeloyl chloride does avoid the problem of tiglate formation; however, the yields are only fair and the applicability of the method would seem to be rather limited.[3,6,7]

While it was clear from these results that base present during the esterification is deleterious, it was also apparent that the group used for angeloyl activation is important. Namely, the group must be capable of imparting sufficient reactivity for angeloyl transfer to take place at a reasonable rate, yet have a conjugate acid that is non-destructive in the absence of base. In addition, the group should not, of course, undergo transfer competitively with the angeloyl moiety.

Two mixed anhydrides **6** and **7**, formed with angelic acid and 2,4,6-trichlorobenzoyl chloride[8] and pivaloyl chloride, respectively, and angelic anhydride (**8**) were evaluated with menthol (**9**) as the test substrate (Table I).[9]

Table I. Esterification of Menthol with Anhydrides 6-8[a]

anhydride	base[b]	time (h)[c]	products, rel%[d]
 6	none	20	menthyl angelate (**10**), 100%
	DMAP	10	**10**, 80%; menthyl tiglate (**11**), 20%
	isoquinoline	13	**10**, 70%; **11**, 30%
 7	none	20	**10**, 50%; menthyl pivalate (**12**), 50%
	DMAP	14	**10**, 10%; **11**, 80%; **12**, 10%
 8	none	20	**9**, 50%; **10**, 50%
	DMAP	17	**10**, 25%; **11**, 75%

[a] Menthol (0.8 M) and 2.0 equiv of the anhydride in dry toluene at 70 °C. [b] 0.2 equiv of base. [c] Approximate time required to consume menthol (except for 6th run). [d] Determined by NMR integration of crude reaction mixture. Products are stable to the reaction conditions.

The mixed anhydride **6** emerged as clearly the best of the three, particularly in the absence of base. Application of this modified Yamaguchi procedure[8] to a wide range of alcohols produced the results given in Table II. As can be seen, the yields are excellent and, in several cases, virtually quantitative. Most notably, *in no example could even a trace amount of the corresponding tiglate ester be detected.* Thus, with this procedure alcohol **1** is selectively converted to homogynolide-A (**2**)[5] and hydroxy ester **3** is now cleanly transformed to the angelate ester **4** (cf. eq 2), without any contamination by the tiglate esters.

This method for converting alcohols to their angelate esters is by far the most effective to date and, consequently, should prove useful for this as well as related[7] purposes.

Esterification of Alcohols with Angelic Acid. General Procedure. To a stirred solution of 0.5 mmol of angelic acid[10] in 0.30 mL of dry toluene under argon was added 0.5 mmol of 2,4,6-trichlorobenzoyl chloride[8] and 0.5 mmol of triethylamine. The resulting mixture was stirred for 2 h at 20 °C and then treated with 0.25 mmol of the alcohol. After being heated at 70-80 °C for 19-36 h (see ref 12), the mixture was allowed to cool to room temperature and was then diluted with 2 mL of ether and filtered. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by dry-column silica gel chromatography[11] to give the pure angelate ester.[12]

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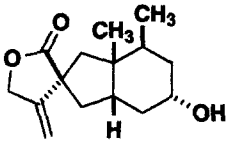
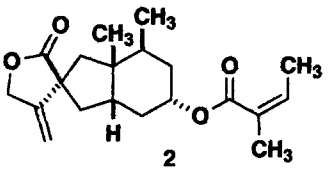
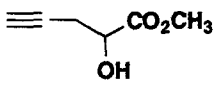
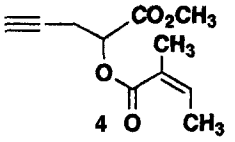
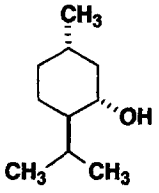
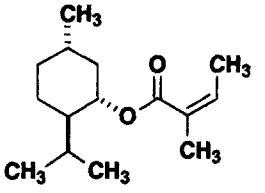
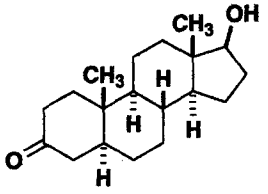
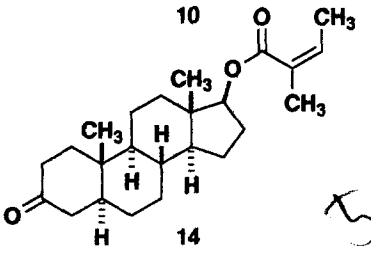
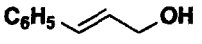
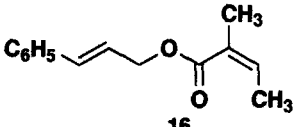
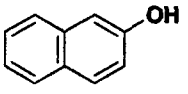
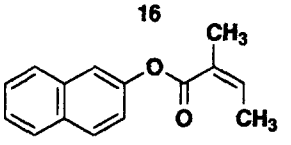
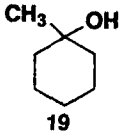
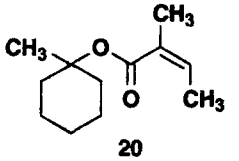
Notes and References

1. Hartmann, B.; Kanazawa, A.; Deprés, J.-P.; Greene, A .E. *Tetrahedron Lett.* **1991**, *32*, 767-768.
2. See, for example: (a) Bohlmann, F.; Tietze, B.-M. *Chem. Ber.* **1970**, *103*, 561-563. (b) Beeby, P. J. *Tetrahedron Lett.* **1977**, 3379-3382. (c) Bal-Tembe, S.; Bhedi, D. N.; J. de Souza, N.; Rupp, R. H. *Heterocycles* **1987**, *26*, 1239-1249. (d) Joseph-Nathan, P.; Cerda, C. M.; Roman, L. U.; Hernandez, J. D. *J. Nat.Prod.* **1989**, *52*, 481-496.
3. Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4056-4068.
4. Hoskins, W. M.; Crout, D. H. G. *J. Chem. Soc. Perkin I* **1977**, 538-544. Nakayama, J.; Nakamura, Y.; Tajiri, T.; Hoshino, M. *Heterocycles* **1986**, *24*, 637-640.

Table II. Conversion of Alcohols to their Angelate Esters[a]

alcohol	angelate ester	yield[b]
 1	 2	97%
 3	 4	80%
 9	 10	95%
 13	 14	91%
 15	 16	92%
 17	 18	96%
 19	 20	65%

[a] Alcohol (0.8 M) and 2.0 equiv of anhydride 6 in dry toluene at 70-80 °C for 19-36 h (see reference 12).

[b] Purified, homogeneous (TLC, NMR) material.

5. Attempted formation of homogynolide-A (2) from 1 with dicyclohexylcarbodiimide and 4-dimethylaminopyridine in toluene at 60 °C gave *only* (NMR) the tiglate ester.
6. Kubo, A.; Nakahara, S.; Inaba, K.; Kitahara, Y. *Chem. Pharm. Bull.* **1985**, *33*, 2582-2584. Dev, V.; Bottini, A. T. *J. Nat. Prod.* **1987**, *50*, 968-971.
7. For relevant studies of the problem of *Z*→*E* isomerization during esterification, see: Roush, W. R.; Blizzard, T .A. *J. Org. Chem.* **1984**, *49*, 1772-1783 and 4332-4339.
8. See: Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem.Soc. Jpn.* **1979**, *52*, 1989-1993. 2,4,6-Trichlorobenzoyl chloride is available from the Aldrich Chemical Company.
9. The mixed anhydride formed with trifluoroacetic anhydride has recently been reported to convert (*E*)-2-methyl-2-butenol to its angelate ester in only 21 % yield. See: Rücker, G.; Mayer, R.; Lee, K. R. *Arch. Pharm.* **1989**, *322*, 821-826.
10. Buckles, R. E.; Mock, G. V. *J. Org. Chem.* **1950**, *15*, 680-684.
11. In cases where the angelate had an Rf value similar to that of anhydride 6, the crude material was stirred for 2 h in 1:1 water-pyridine (1 mL) and then extractively isolated, prior to chromatographic purification.

12. **Homogynolide-A (2).** Prepared in 97 % yield by reaction at 70 °C for 16 h. ^{1}H NMR δ 0.90 (d, J=6.9 Hz, 3H), 1.02 (s, 3H), 1.45-2.00 (m, 7H), 1.85 (dq, J=1.1, 1.4 Hz, 3H), 1.99 (dq, J=1.4, 6.6 Hz, 3H), 2.10 (dd, J=5.8, 12.0 Hz, 1H), 2.25-2.40 (m, 1H), 2.40-2.50 (m, 1H), 4.77 (m, 2H), 5.02 (s, 1H), 5.09 (s, 1H), 5.17 (m, 1H), 6.05 (qq, J=1.1, 6.6 Hz, 1H); ^{13}C NMR δ 15.7 (CH_3), 15.9 (CH_3), 18.8 (CH_3), 20.8 (CH_3), 27.4 (CH_2), 28.7 (CH), 34.2 (CH_2), 43.6 (C), 44.6 (CH), 44.7 (CH_2), 48.8 (CH_2), 49.8 (C), 69.6 (CH), 70.3 (CH_2), 105.5 (CH_2), 127.9 (C), 138.1 (CH), 150.5 (C), 167.1 (C), 182.5 (C); IR 1780, 1710, 1670, 1645 cm^{-1}; mass spectrum (CI), m/e 350 (MH^++ammonia, 100%), 333 (MH^+), 250, 233, 122, 110. Anal. Calcd for $C_{20}H_{28}O_4$: M_r , 332.1988. Found: M_r (mass spectrum), 332.1985. **(*Z*)-(1-Methoxycarbonyl-3-butynyl) 2-Methyl-2-butenoate (4).**[2a] Prepared in 80 % yield by reaction at 80 °C for 20 h. ^{1}H NMR δ 1.92 (t, J=5.8 Hz, 1H), 1.95 (s, 3H), 2.03 (d, J=7.0 Hz, 3H), 2.82 (dd, J=5.8, 6.0 Hz, 2H), 3.79 (s, 3H), 5.26 (t, J=6.0 Hz, 1H), 6.17 (q, J=7.0 Hz, 1H); ^{13}C NMR δ 15.9 (CH_3), 20.3 (CH_3), 21.7 (CH_2), 52.5 (CH_3), 70.0 (CH), 71.1 (C), 78.1 (CH), 126.9 (C), 139.8 (CH), 166.9 (C), 169.1 (C); IR 3300, 2950, 2130, 1770, 1730, 1645, 1140, 840 cm^{-1}; mass spectrum (CI), m/e 228 (MH^++ammonia), 211 (MH^+), 124 (100%), 110, 83. **(*Z*)-[(1S, 2R, 5S)-2-Isopropyl-5-methylcyclohexyl] 2-Methyl-2-butenoate (10).** Prepared in 95 % yield by reaction at 70 °C for 20 h. $[\alpha]^{20}_D$ - 84.6° (c 1, $CHCl_3$); ^{1}H NMR δ 0.75 (d, J=6.9 Hz, 3H), 0.88 (d, J=7.1 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H), 1.00-1.80 (m, 9H), 1.86 (dq, J=1.3, 1.4 Hz, 3H), 1.94 (dq, J=1.3, 7.5 Hz, 3H), 4.75 (td, J=4.1, 11.0 Hz, 1H), 5.98 (qq, J=1.4, 7.5 Hz, 1H); ^{13}C NMR δ 15.6 (CH_3), 16.2 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.4 (CH_2), 26.3 (CH), 31.4 (CH), 34.3 (CH_2), 41.1 (CH_2), 47.1 (CH), 73.8 (CH), 128.5 (C), 136.6 (CH), 167.7 (C); IR 2950, 1715, 1650, 1230, 1160 cm^{-1}; mass spectrum (CI), m/e 256 (MH^++ammonia), 239, 139, 124 (100%), 110, 83, 75. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.43; H, 11.05. **Angelate Ester of 5α-Androstan-17β-ol-3-one (14).** Prepared in 91 % yield by reaction at 70 °C for 23 h. Mp 103-105 °C (hexane); $[\alpha]^{20}_D$ + 45.0° (c 0.5, $CHCl_3$); ^{1}H NMR δ 0.70-2.40 (m, 22H), 0.85 (s, 3H), 1.02 (s, 3H), 1.89 (dq, J=1.3, 1.4 Hz, 3H), 1.98 (dq, J=1.3, 7.0 Hz, 3H), 4.66 (t, J=7.5 Hz, 1H), 6.04 (qq, J=1.4, 7.0 Hz, 1H); ^{13}C NMR 11.4 (CH_3), 12.4 (CH_3), 15.7 (CH_3), 20.6 (CH_3), 20.8 (CH_2), 23.5 (CH_2), 27.7 (CH_2), 28.7 (CH_2), 31.1 (CH_2), 35.1 (CH), 35.6 (C), 36.9 (CH_2), 38.0 (CH_2), 38.4 (CH_2), 42.7 (C), 44.5 (CH_2), 46.5 (CH), 50.5 (CH), 53.7 (CH), 82.6 (CH), 128.2 (C), 137.1 (CH), 168.0 (C), 211.7 (C); IR 1725, 1710, 1230, 1160 cm^{-1}; mass spectrum (CI), m/e 390 (MH^++ammonia, 100%), 373 (MH^+), 290, 273, 83. **(*Z*)-[(*E*)-3-Phenyl-2-propenyl] 2-Methyl-2-butenoate (16).** Prepared in 92 % yield by reaction at 70 °C for 19 h. ^{1}H NMR δ 1.92 (dq, J=1.3, 1.4 Hz, 3H), 2.00 (dq, J=1.3, 7.4 Hz, 3H), 4.81 (d, J=6.2 Hz, 2H), 6.09 (qq, J=1.3, 7.4 Hz, 1H), 6.33 (dt, J=6.2, 15.8 Hz, 1H), 6.68 (d, J=15.8 Hz, 1H), 7.20-7.50 (m, 5H); ^{13}C NMR δ 15.7 (CH_3), 20.5 (CH_3), 64.6 (CH_2), 123.5 (CH), 126.5 (CH), 127.8 (C), 128.2 (CH), 128.5 (CH), 133.8 (CH), 136.3 (C), 138.0 (CH), 167.7 (C); IR 3080, 3050, 3010, 2950, 1720, 1650, 1440, 1220 cm^{-1}; mass spectrum (EI), m/e 216 (M^+), 117, 83, 55 (100%), 28. **(*Z*)-(2-Naphthyl) 2-Methyl-2-butenoate (18).** Prepared in 96 % yield by reaction at 70 °C for 36 h. ^{1}H NMR δ 2.07-2.15 (m, 3H), 2.10 (s, 3H), 6.29 (m, 1H), 7.26 (dd, J=2.7, 8.9 Hz, 1H), 7.45-7.55 (m, 2H), 7.59 (d, J=2.1 Hz, 1H), 7.75-7.95 (m, 3H); ^{13}C NMR δ 18.0 (CH_3), 20.7 (CH_3), 118.6 (CH), 121.4 (CH), 125.6 (CH), 126.5 (CH), 127.3 (C), 127.6 (CH), 127.7 (CH), 129.3 (CH), 131.4 (C), 133.8 (C), 140.7 (CH), 148.4 (C), 166.3 (C); IR 3100, 2930, 2920, 1730, 1650, 1630, 1600, 1510, 1120 cm^{-1}; mass spectrum (EI), m/e 226 (M^+), 144, 115, 83, 55 (100%) . **(*Z*)-(1-Methylcyclohexyl) 2-Methyl-2-butenoate (20).** Prepared in 65 % yield by reaction at 80 °C for 20 h. ^{1}H NMR δ 1.20-1.60 (m, 10H); 1.52 (s, 3H), 1.88 (s, 3H), 1.95 (d, J=6.8 Hz, 3H), 5.55 (q, J=6.8 Hz, 1H); ^{13}C NMR δ 15.5 (CH_3), 20.9 (CH_3), 22.1 (CH_2), 25.4 (CH_2), 25.7 (CH_3), 36.8 (CH_2), 81.8 (C), 129.7 (C), 135.5 (CH), 167.4 (C); IR 2985, 2850, 1720, 1640, 1140, 840 cm^{-1}.

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