# IMPROVED SYNTHESIS OF (±)-PRAERUPTORIN A AND OTHER KHELLACTONE ESTERS BY SOLVENT-FREE DCC REACTIONS§

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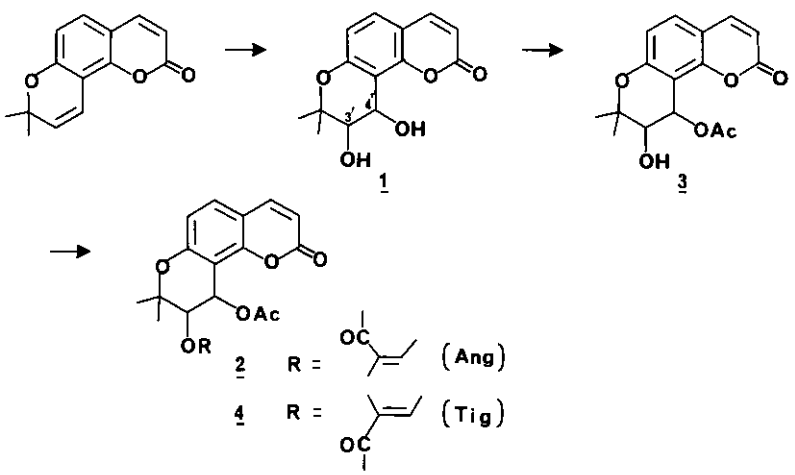
Abstract - Esters of 4'-acetylkhellactone such as (±)-praeruptorin A (2) were synthesised in considerably improved yields through use of a low temperature solvent-free DCC esterification reaction.

In a previous paper[1] we described a method for the synthesis of mono- and diacyl derivatives of khellactone (1) and its application to the total synthesis of the pyranocoumarin natural product (±)-praeruptorin A (=Pd-Ia) (2), claimed to be a calcium antagonist[2] (Scheme I). Although we were successful in obtaining the target compound, the final step of the synthesis namely

Scheme I




acylation of 3 with angelic acid and DCC in refluxing dichloromethane left much to be desired. The yield of the reaction was very low (4.6 %) and starting material was not completely consumed even after the reaction mixture was refluxed for 1.25 days. The other serious problem was isomerisation about the double bond leading to the undesired tiglate ester 4 as the major product (11:1, tiglate:angelate).

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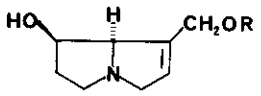
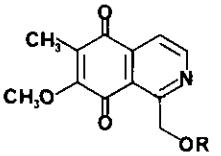
§*Dedicated to Dr. E. Baltin, Managing Director, Hoechst India Limited, on the occasion of his completion of 25 years with Hoechst AG., West Germany.*

Low yields and isomerisation during the formation of angelate esters are problems frequently encountered in the literature[3]. In the preparation of semisynthetic esters of retronecine (5), treatment of 5 with angelic acid/DCC gave only a 13% yield of ester 6 (4:1 ratio of 6a:6b)[4]. Again in the synthesis of the antimicrobial metabolite renierone (7)[5], attempted esterification




5 R = H
6a R = Ang
6b R = Tig




7 R = Ang
8 R = H
9 R = Tig

of intermediate 8 with angeloyl chloride/pyridine failed to give 7, providing instead tiglate 9 in 35% yield. Under identical conditions other acid chlorides reacted smoothly to give high yields of esters. The authors had to resort to esterification via phenyllithium/angeloyl chloride to obtain the angelate 7 in 38% yield. These conditions however are not very mild and the use of phenyllithium may not be suitable for sensitive substrates.

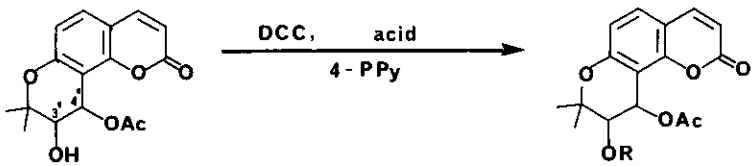
*The angelate group is frequently encountered in bioactive natural products*[6]. *The paucity of high-*yielding methods for the synthesis of angelate esters as well as our need for an economically viable synthesis of (+)-praeruptorin A led us to further investigate the carboxylic acid/DCC procedure[7]. Our requirements were twofold : 1) To ensure complete conversion of starting alcohol to ester 2) to minimise isomerisation to tiglate. Our results are described below.

When a solution of 0.5 mmol of cis-hydroxy acetate 3, 1.62 mmol of angelic acid[8] and 2.8 mmol of DCC in 25 ml of dry dichloromethane containing 0.03 mmol of 4-pyrrolidinopyridine was stirred at room temperature for 1.75 h, a trace of product ester could be detected on tlc, and a white solid began separating out of solution. At this stage the precipitate, later identified as N,N'-dicyclohexylurea, was rapidly filtered off and the filtrate evaporated to dryness in vacuo, the flask tightly stoppered and left in the refrigerator at ca. 8°C[9]. The reaction was monitored twice daily. After 2.5 days, tlc showed complete disappearance of starting material[10]. Chromatography of the crude material gave the ester 2 in 42% yield (an equivalent amount of tiglate ester 4 was also formed). The ratio of angelate to tiglate esters was improved to 1:1 as compared with 1:11 in the previously described solution reaction and starting material was completely consumed. As a result an improved synthesis of (+)-praeruptorin A was achieved in 42% yield in comparison with our earlier synthesis in 4.6% yield[1].

Following the procedure described above, the new low temperature solvent-free DCC reaction was applied to the synthesis of other compounds in the khellactone ester series. The results are summarised in Table I. Worth particular mention is the preparation of the tiglate ester 4 in 75% yield as compared with the earlier reported yield of 46% in the solution reaction where a lot of unreacted starting material was recovered after 5.25 days in refluxing dichloromethane[1]. Esters of trans-hydroxy acetate 10[1] were also obtained in high yields using our new solvent-free esterification conditions.

Table I

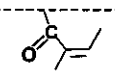
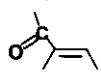
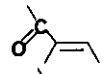
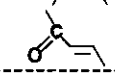
Acylation of Hydroxy Acetates 3 and 10




3 3'-4' cis

10 3'-4' trans

2, 4, 11, 12

| Compound No. | R | 3'-4' stereochemistry | $CH_2Cl_2$ (reflux) Time (days) | $CH_2Cl_2$ (reflux) Yield % | Solvent-free Time (days) | Solvent-free Yield % | mp (°C)[a] |
|---|---|---|---|---|---|---|---|
| 2[b] |  | cis | 1.25 | 4.6[c] | 2.5 | 42[d] | 145-147.5 |
| 4[b] |  | cis | 5.25 | 46.6 | 3 | 75 | 147-149 |
| 11[e] |  | trans | - | - | 2.5 | 94 | 158-160 |
| 12[e] |  | trans | - | - | 1.75 | 82 | 180-182 |

(a) Satisfactory nmr, ir and analytical (C, H, O) data were obtained (cf. Experimental) for all compounds listed in the table. Melting points are uncorrected.

(b) From cis-hydroxy acetate 3[1].

(c) 52 % of 4 was also obtained.

(d) 43 % of 4 was also obtained.

(e) From trans-hydroxy acetate 10[1].

In summary, we have achieved an improved synthesis of (±)-praeruptorin A (2) and introduced a new high-yielding modification of the DCC esterification reaction which should find application in the synthesis of esters which may not be readily available by conventional methods. The reaction has scope for an in-depth investigation and a definitive mechanism awaits further study.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. $^1$H-Nmr spectra were recorded on a JEOL-90-Q spectrometer. Chemical shifts are reported in $\delta$ units downfield from the internal standard tetramethylsilane. The coupling constants (J) are in Hertz. Ir spectra were recorded on a Perkin Elmer 157 spectrophotometer and are reported in reciprocal centimetres ($cm^{-1}$).

Compounds 3 and 10 were prepared as previously reported[1]. Conditions for the esterification of 3 in refluxing dichloromethane have been described earlier[1]. The procedure for the reaction under solvent-free conditions is described below.

Typical Procedure for the Esterification of Acetylkhellactones 3 and 10 (Table I)

(+)-Praeruptorin A (2) : A solution of cis-acetylkhellactone 3 (0.156 g, 0.5 mmol), angelic acid[8] (0.162 g, 1.62 mmol), DCC (0.57 g, 2.8 mmol) and 4-pyrrolidinopyridine (0.0045 g, 0.03 mmol) in dry $CH_2Cl_2$ (25 ml) was stirred at room temperature for 1.75 h. A white solid which separated out was filtered off and the filtrate evaporated to dryness in vacuo. The flask was tightly stoppered and kept in the refrigerator at ca. 8°C. The reaction was monitored twice daily by tlc. After 2.5 d the reaction was complete. Flash chromatography of the product on silica gel with gradient elution (petroleum ether-EtOAc) gave first the angelate ester 2 (0.084 g, 42%), mp 145-147.5°C[11] (cyclohexane). Later column fractions furnished the tiglate ester 4 (0.086 g, 43%), mp 147-149°C (cyclohexane) (lit[1]. mp 147-149°C). The ir and $^1$H-nmr spectra for 2 and 4 were identical to those previously reported[1] for these compounds. Anal. Calcd for $C_{21}H_{22}O_7$ : C, 65.27; H, 5.74. Found : C, 65.61; H, 5.82.

The following compounds were prepared according to the typical procedure described above.

(+)-cis-4'-O-Acetyl-3'-O-tigloylkhellactone (= (+)-cis-10-Acetoxy-9,10-dihydro-8,8-dimethyl-9-[(E)-2-methyl-2-butenoyloxy]-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one)[13] (4) : Compound 4 was prepared from compound 3 and tiglic acid in 75% yield. The mp, ir and nmr spectra were identical in all respects with those reported[1] for compound 4. Anal. Calcd for $C_{21}H_{22}O_7$ : C, 65.27; H, 5.74. Found : C, 65.46; H, 5.68.

(+)-trans-4'-O-Acetyl-3'-O-tigloylkhellactone (11) : Compound 11 was prepared from compound 10 and tiglic acid in 94% yield ; mp 158-160°C (cyclohexane); ir (KBr) : 1610, 1720, 1750, 2985; $^1$H-nmr ($CDCl_3$) : 7.52 (1H, d, J = 10.08, H-C(4)), 7.28 (1H, d, J = 9.0, H-C(5)), 6.76 (1H, m, $CH_3C$=C$H$C$H_3$), 6.74 (1H, d, J = 9.0, H-C(6)), 6.21 (1H, d, J = 5.04, H-C(4')), 6.16 (1H, d, J = 10.08, H-C(3)), 5.30 (1H, d, J = 5.04, H-C(3')), 2.08 (3H, s, -OCOC$H_3$), 1.80 (3H, s, C$H_3$C=CHC$H_3$), 1.77 (3H, bd, J = 9.0, $CH_3C$=CHC$H_3$), 1.34 and 1.42 (each 3H, s, 2 X $CH_3$-C(2')). Anal. Calcd for $C_{21}O_{22}O_7$ : C, 65.27; H, 5.74. Found : C, 65.21; H, 5.44.

(+)-trans-4'-O-Acetyl-3'-O-[(E)-2-butenoyl]khellactone (12) : Compound 12 was prepared from compound 10 and crotonic acid in 82% yield; mp 180-182°C (EtOAc-petroleum ether); ir (KBr) : 1610, 1720, 1735, 1755, 2990; $^1$H-nmr ($CDCl_3$) : 7.55 (1H, d, J = 9.72, H-C(4)), 7.29 (1H, d, J = 8.28, H-C(5)), 6.96 (1H, dq, J = 15.0 and 7.0, -CH=C$H$CH$_3$) 6.75 (1H, d, J = 8.28, H-C(6)), 6.20 (1H, d, J = 5.04, H-C(4'), 6.16 (1H, d, J = 9.72, H-C(3)), 5.78 (1H, dq, J = 15.0 and 2.0, -C$H$=CHCH$_3$), 5.29 (1H, d, J = 5.04, H-C(3')), 2.13 (3H, s, -OCOC$H_3$), 1.88 (3H, dd, J = 7.0 and 2.0, -CH=CHC$H_3$), 1.37 and 1.45 (each 3H, s, 2 X $CH_3$-C(2')). Anal. Calcd for $C_{20}H_{20}O_7$ : C, 64.51; H, 5.41. Found : C, 64.70; H, 5.29.

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9. In more recent experiments we have found :
   a) filtration of N,N'-dicyclohexylurea is not necessary.
   b) the reaction works as well if the reagents are dissolved in dichloromethane and the reaction mixture immediately evaporated to dryness and left in the refrigerator.
10. In comparison, when the reaction mixture in dichloromethane solution with or without filtration of urea was left at room temperature or refluxed for 5 days not more than 60% of starting alcohol was converted to product ester.
11. The melting point of compound 2 was not depressed on admixture with an authentic sample[12] of (±)-praeruptorin A (=Pd-Ia) which melted at 144.5-147°C.
12. We thank Professor S. Shibata, Department of Pharmacognosy and Phytochemistry, Meiji College of Pharmacy, Tokyo, Japan, for sending us a sample of (±)-praeruptorin A (=Pd-Ia) for comparison.
13. Representative IUPAC nomenclature.

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