Expeditious and enantiospecific avenue to pentacyclic quassinoid skeleton

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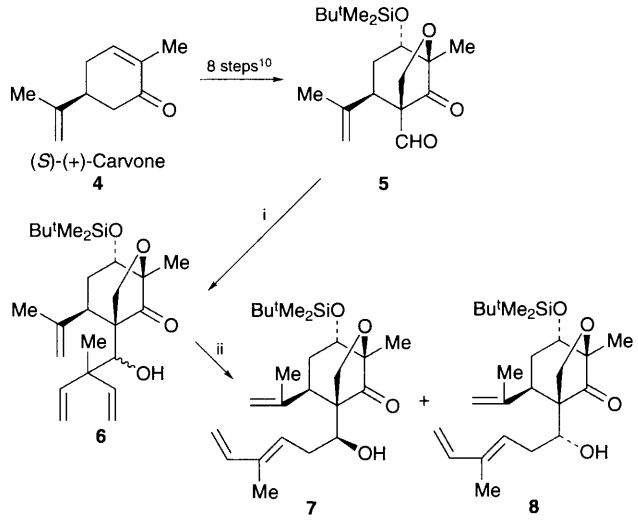
The pentacyclic quassinoid skeleton 3 is constructed from (*S*)-carvone involving a 1,3-sigmatropic rearrangement and an intramolecular Diels–Alder reaction as the key steps.

The quassinoids,[1] a large group of terpenoid bitter principles extracted from the plant *Simaroubaceae*,[2] display a wide spectrum of biological properties.[1,3] Their intriguing tetracyclic or pentacyclic carbon frameworks, comprising a number of contiguous stereocentres and oxygen functionalities, pose a formidable synthetic challenge and are elusive target molecules.[4] The pioneer and the major contributor in this area of research are the group led by Grieco, producing impressive and elegant total syntheses of a number of tetracyclic and pentacyclic members.[5] Among the quassinoids, simalikalactone D **1**[6] and quassimarin **2**[7] are of considerable interest because they are cytotoxic and display potent activity *in vivo* against the P-388 lymphocytic leukaemia in mice (PS).[8] Recent findings have indicated that **1** and **2** possess marked differential solid tumour selectivity.[8] Structurally, both compounds share an ABCDE ring system **3** with common stereochemical features, but possessing different butyrate esters at C-15.

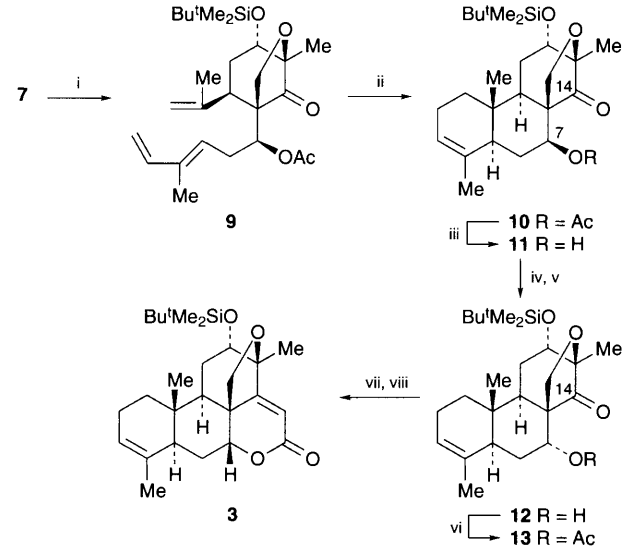
In our quest for a first enantiospecific entry to simalikalactone D **1** and quassimarin **2**, we are interested in the construction of the pentacyclic skeleton **3** that contains seven stereogenic centres. Our synthetic strategy is based on the C→CE→ABCE→ABCDE ring annulation sequence. We previously reported a convergent synthesis of a tetracyclic quassinoid skeleton through a series of regioselective and stereocontrolled reactions from (+)-carvone.[9] As an extension of this approach, this communication now describes rapid access to homochiral skeleton **3** as a suitable intermediate for further elaboration into the target molecules, involving a 1,3-sigmatropic rearrangement and an intramolecular Diels–Alder (IMDA) reaction as the key steps.

Our recent work[10] has indicated that (+)-carvone **4** could be easily transformed into keto aldehyde **5**, which possesses the epoxymethano bridge (ring E), in eight steps with an overall yield of 47%. The assembly of a six-carbon diene component onto **5** to form an IMDA precursor demanded considerable experimentation. Eventually, a rewarding two-step reaction sequence was found. Thus, addition of the Grignard reagent derived from 5-bromo-3-methylpenta-1,2-diene[11] to **5** afforded adduct **6**† as the sole product (Scheme 1). This was followed by a 1,3-sigmatropic rearrangement[12] which occurred smoothly in the presence of sodium hydride to give a mixture of IMDA precursors **7**, mp 90–91 °C, $[\alpha]_D^{20}$ +38 (*c* 2.0, CH_2Cl_2) and **8**, $[\alpha]_D^{20}$ +68 (*c* 0.7, CH_2Cl_2), in a ratio of 10 : 1, respectively.‡

The keto alcohol **7** experienced a retro-aldol reaction on heating and the free hydroxy group had to be protected as



Scheme 1 *Reagents and conditions*: i, Mg, 5-bromo-3-methylpenta-1,3-diene, Et_2O, −10 °C, 80%; ii, NaH, 18-Crown-6, THF, room temp., 18 h, 85% (**7**:**8** = 10:1)



Scheme 2 *Reagents and conditions*: i, Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temp., 16 h, 100%; ii, sealed tube, toluene, 170 °C, 110 h, 100%; iii, NaOH, MeOH, room temp., 12 h, 96%; iv, Dess–Martin periodinane, CH_2Cl_2, room temp., 6 h, 96%; v, K-Selectride, THF, room temp., 20 min, 97%; vi, Ac_2O, DMAP, CH_2Cl_2, room temp., 16 h, 100%; vii, LDA, toluene–THF (5 : 1), −78 °C, 30 min, 87%; viii, $SOCl_2$, pyridine, CH_2Cl_2, room temp., 20 h, 90%

acetate **9**, mp 80–82 °C; $[\alpha]_D^{20}$ +54 (*c* 2.0, CH_2Cl_2), before being subject to a [4 + 2] cycloaddition reaction (Scheme 2). Upon heating in a sealed tube, the triene acetate **9** underwent a thermodynamically-controlled IMDA[13] reaction to furnish, in quantitative yield, the *trans*-fused ABCE ring system **10**, $[\alpha]_D^{20}$ +130 (*c* 0.4, CH_2Cl_2). At this stage, the undesired stereochemistry at C-7 needed to be rectified. Thus deacetylation of the ester in the tetracycle **10** gave β-alcohol **11**, $[\alpha]_D^{20}$ + 78 (*c* 2.6, CH_2Cl_2). The configuration of the hydroxy group was inverted by an efficient oxidation–reduction sequence. Oxidation was best conducted with Dess–Martin periodinane[14] and reduction was *via* equatorial attack with K-Selectride, leading to the desired α-alcohol **12** with an overall yield of 93%, mp 105–107 °C, $[\alpha]_D^{20}$ +75 (*c* 2.7, CH_2Cl_2). It is noteworthy that the hydride reduction was highly regioselective, leaving the C-14 carbonyl group intact.

Formation of the final lactone D ring required the introduction of an acetyl group onto the free alcohol in **12**. Hence, the alcohol **12** was esterified into acetate **13**, mp 145–147 °C, $[\alpha]_D^{20}$ +14.2 (*c* 1.4 in CH_2Cl_2).§ The structure and stereochemistry of **13** were confirmed by a single crystal X-ray analysis.¶ Enolisation of the acetyl group in **13** with lithium diisopropylamide (LDA) caused an intramolecular aldolization to occur, giving the corresponding aldol which underwent smooth β-elimination to the pentacyclic skeleton **3**, mp 186–188 °C; $[\alpha]_D^{20}$ −38 (*c* 0.5, CH_2Cl_2).

In summary, we have presented a short, convergent, stereocontrolled and enantiospecific synthesis of pentacycle **3** with functionalities suitable for further elaboration to optically active simalikalactone D **1** and quassimarin **2**. Research in this direction is under active investigation.

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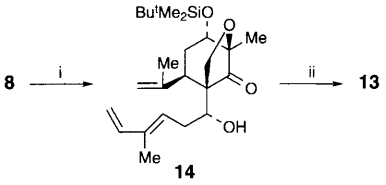
Footnotes

† All new compounds gave satisfactory analytical and spectral data. *Selected NMR data* for **3**: δ_H(500 MHz, [$^2H_6$]benzene) 0.001 (s, 3 H), 0.02 (s, 3 H), 0.72 (s, 3 H), 0.92–1.01 (m, 11 H), 1.35 (s, 3 H), 1.45 (m, 2 H), 1.55 (dd, *J* 3.0 and 13.7, 1 H), 1.61 (s, 3 H), 1.80 (dt, *J* 13.5, 1 H), 1.90–1.94 (m, 2 H), 2.00 (dt, *J* 14.5, 1 H), 2.45 (br d, *J* 13.2, 1 H), 3.23 (d, *J* 8.4, 1 H), 3.80 (br s, 1 H), 4.06 (br s, 1 H), 4.21 (d, *J* 8.4, 1 H), 5.33 (s, 1 H), 5.81 (s, 1 H); δ_C(250 MHz, $CDCl_3$) −5.0, −4.4, 11.8, 17.4, 17.8, 21.2, 22.3, 25.6, 27.4, 34.4, 34.7, 40.7, 46.9, 47.1, 72.1, 77.3, 79.0, 82.9, 107.4, 121.3, 133.1, 164.3, 167.1. For **13**: δ_H(500 MHz, [$^2H_6$]benzene) −0.07 (s, 3 H), −0.04 (s, 3 H), 0.71 (s, 3 H), 0.89 (m, 1 H), 0.95 (s, 9 H), 1.19 (m, 1 H), 1.29 (s, 3 H), 1.50–1.58 (m, 5 H), 1.75 (br d, *J* 14.4, 1 H), 1.89 (m, 2 H), 1.97–2.06 (m, 4 H), 2.26 (dd, *J* 4.3 and 13.4, 1 H), 2.62 (br d, *J* 13.4, 1 H), 3.46 (d, *J* 8.8, 1 H), 3.86 (br s, 1 H), 4.29 (d, *J* 8.8, 1 H), 5.27 (br s, 1 H), 5.58 (br s, 1 H); δ_C (62.9 MHz, $CDCl_3$) −5.1, −4.4, 12.7, 15.9, 17.8, 21.2, 21.3, 22.5, 25.5, 27.7, 35.3, 36.4, 40.2, 44.8, 51.5, 68.3, 69.2, 78.3, 79.8, 121.0, 133.7, 170.4, 201.3.

‡ Attempts to obtain the triene **7** or **8** directly from keto aldehyde **5** using various synthetic equivalents of 3-methylpenta-2,4-dienyl carbanion were fruitless.

§ Tetracycle **13** could also be obtained from triene alcohol **8** in two steps with an overall yield of 82% (Scheme 3).



Scheme 3 *Reagents and conditions*: i, Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temp. 16 h, 96%; ii, sealed tube, toluene, 170 °C, 110 h, 85%

¶ *Crystal data* for **13**: $C_{26}H_{42}O_5Si$, crystal dimensions 0.1 × 0.4 × 0.45 mm, M = 462.7, orthorhombic, space group $P2_12_12_1$, a = 9.963(7), b = 14.302(2), c = 19.443(3) Å, V = 2770(2) Å^3, Z = 4, D_c = 1.109 Mg m^{-3}, $F(000)$ = 1008, λ(Mo-Kα) = 0.71073 Å, R = 0.065, R_w = 0.060, S = 1.65 for 1167 observed [$|F_o| \geqslant 4\sigma|F_o|$]. Structure solution and refinement were carried out on a 486 PC using SHELXTL-PC. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request from the CCDC for this information should cite the full literature reference and the reference no. 182/228.

References

1 J. Polonsky, *Fortschr. Chem. Org. Naturst.*, 1985, **47**, 221; 1973, **30**, 101.
2 Examples of some recently isolated quassinoids, see: K. Koike, M. Yokoh, M. Furukawa, S. Ishii and T. Ohmoto, *Phytochemistry*, 1995, **40**, 233; P. A. Grieco, J. M. VanderRoest, M. M. Pineironunez, E. E. Campaigne and M. Carmack, *Phytochemistry*, 1995, **38**, 1463; Y. Ouyang, K. Mitsunaga, K. Koike and T. Ohmoto, *Phytochemistry*, 1995, **39**, 911.
3 P. W. Grosvenor, P. K. Gothard, N. C. Mcwilliam, A. Supriono and D. O. J. Gray, *J. Ethnopharmacol.*, 1995, **45**, 75; Z. Lidert, K. Wing, J. Polonsky, Y. Imakurra, M. Okano, S. Tani, Y.-M. Lin, H. Kiyokawa and K.-H. Lee, *J. Nat. Prod.*, 1987, **50**, 442; J. Polonsky, in *The Chemistry and Chemical Taxonomy of the Rutales*; eds. P. G. Waterman and M. F. Grandon, Academic Press, New York, 1983, p. 247.
4 Examples of some recent synthetic work, see: C. K.-F. Chiu, S. V. Govindan and P. L. Fuchs, *J. Org. Chem.*, 1994, **59**, 311; C. Spino, G. Liu, N. Tu and S. Girard, *J. Org. Chem.*, 1994, **59**, 5596; C. Spino and N. Tu, *Tetrahedron Lett.*, 1994, **35**, 3683; C. Spino and G. Liu, *J. Org. Chem.*, 1993, **58**, 817; H. Stojanac and Z. Valenta, *Can. J. Chem.*, 1991, **69**, 853; M. Sasaki, T. Murae and T. Takahashi, *J. Org. Chem.*, 1990, **55**, 528; M. Kim, K. Kawada, R. S. Gross and D. S. Watt, *J. Org. Chem.*, 1990, **55**, 504; K. Kawada, M. Kim and D. S. Watt, *Tetrahedron Lett.*, 1989, **30**, 5985. Earlier synthetic efforts are described in K. Kawada, M. Kim and D. S. Watt, *Org. Prep. Proced. Int.*, 1989, **21**, 521.
5 P. A. Grieco and M. M. Piñeiro-Nuñez, *J. Am. Chem. Soc.*, 1994, **116**, 7606; P. A. Grieco, J. L. Collins, E. D. Moher, T. J. Fleck and R. S. Gross, *J. Am. Chem. Soc.*, 1993, **115**, 6078; P. A. Grieco and J. M. VanderRoest, *J. Am. Chem. Soc.*, 1993, **115**, 5841; T. J. Fleck and P. A. Grieco, *Tetrahedron Lett.*, 1992, **33**, 1813; P. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, 1990, **112**, 4595.
6 J.-P. Tresa, L. Alais and J. Polonsky, *C. R. Seances Acad. Sci., Ser. C*, 1971, **273**, 601.
7 S. M. Kupchan and D. R. Streelman, *J. Org. Chem.*, 1976, **41**, 3481.
8 E. D. Moher, P. A. Grieco and J. L. Collins, *J. Org. Chem.*, 1993, **58**, 3789; E. D. Moher, J. L. Collins and P. A. Grieco, *J. Am. Chem. Soc.*, 1992, **114**, 2764.
9 T. K. M. Shing, Y. Tang, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1625; *J. Chem. Soc., Chem. Commun.*, 1992, 341; *Tetrahedron*, 1990, **46**, 2187; T. K. M. Shing, Y. Tang and J. F. Malone, *J. Chem. Soc., Chem. Commun.*, 1989, 1294.
10 T. K. M. Shing, X. Y. Zhu and T. C. W. Mak, *Tetrahedron: Asymmetry*, 1996, **7**, 673.
11 K. B. Clark, P. N. Culshaw, D. Griller, F. P. Lossing, J. A. Martinho Simões and J. C. Walton, *J. Org. Chem.*, 1991, **56**, 5535; G. Buchi and H. Wuest, *J. Am. Chem. Soc.*, 1974, **96**, 7573.
12 S. R. Wilson, D. T. Mao, K. M. Jernberg and S. T. Ezmirly, *Tetrahedron Lett.*, 1977, 2559.
13 For a recent example of thermodynamically-controlled IMDA reaction, see T. K. M. Shing and J. Yang, *J. Org. Chem.*, 1995, **60**, 5785. For a review on IMDA reactions, see W. R. Roush, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, p. 513.
14 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.

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