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A rearrangement–cycloaddition approach to spiro-fused indanones

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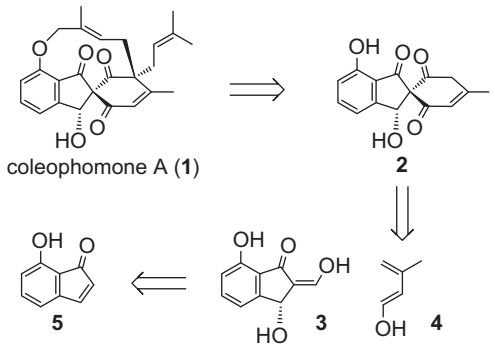
ABSTRACT

Spiro-fused indanones were constructed using a [4 + 2]-cycloaddition approach from α-methylene indanone dienophiles, which were elaborated from 4-chromanone in a number of steps including a key rearrangement process. This type of spiro-fused structure forms the central core ring system found in natural products such as coleophomone A. The cycloaddition reactions using an α-methylene indanone dienophile led to the *exo* diastereoisomer as the major cycloadduct, whereas the 1,4-dione based dienophile predominantly led to the *endo* diastereoisomer.

The spiro-fused indanone unit, such as **2**, is a structurally unique ring system found at the core of the natural products coleophomone A (**1**)[1] and fredericamycin A.[2] The construction of these complex structures represents a synthetic challenge,[3] which could be achieved via a cycloaddition approach using α-methylene indanones. Reports of the hetero-Diels–Alder based assembly of spiro-fused heterocyclic structures analogous to **2** have been limited to reactions between α-oxo sulfine derivatives of indanones and 1,3-dienes,[4] or 2-hydroxymethylene indanones and either α-nitro- or α-azo-styrene.[5]

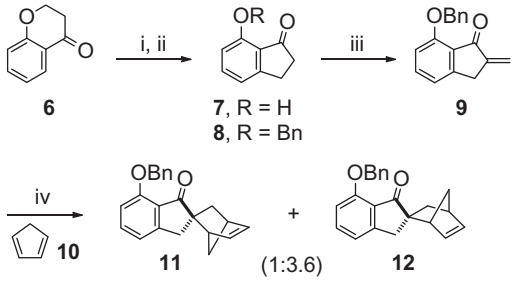
Therefore, based on this precedent and our interest in the development of a synthesis of these structures, with applications in target synthesis, we describe preliminary studies which have led to a rearrangement–cycloaddition approach to spiro-fused indanones.



Scheme 1. Retrosynthetic analysis of coleophomone A (**1**) and the embedded spiro-fused indanone core structure **2**.

The antibacterial natural product coleophomone A (**1**), isolated from the plant fungus *Coleophoma* sp.,[1,6,7] possesses an 11-membered cyclic ether with an embedded spiro-fused indanone. Simplification of this intriguing natural structure reveals the core ring system **2** (Scheme 1). Next, a retro-cycloaddition disconnection on **2** leads to the dienophile **3** and the diene **4**. Finally, the substituted indanone **3** could be elaborated from the indenone **5**. Thus, our retrosynthetic analysis reveals a unique opportunity for the development of a [4 + 2]-cycloaddition approach to the spiro-fused indanone core found in coleophomone A (**1**).

Our plan for the construction of spiro-fused indanone structures demanded the preparation of α-methylene substituted indanone-based dienophiles, such as **9**, which could be elaborated from commercially available 4-chromanone (**6**). The first step in our



Scheme 2. Reagents and conditions: (i) $AlCl_3$, 180 °C, 20 min; then 200 °C, 30 min, 75% (**7**); (ii) BnBr, TBAI, K_2CO_3, DMF, 99% (**8**); (iii) $(CH_2O)_n$, morpholine, AcOH, 80 °C, 93%; (iv) cyclopentadiene (**10**), toluene, 120 °C, 79% combined yield (**11**:**12**, 1:3.6).

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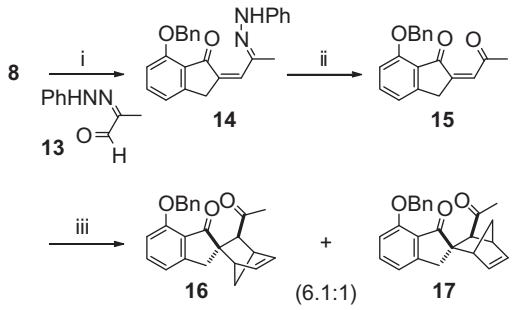
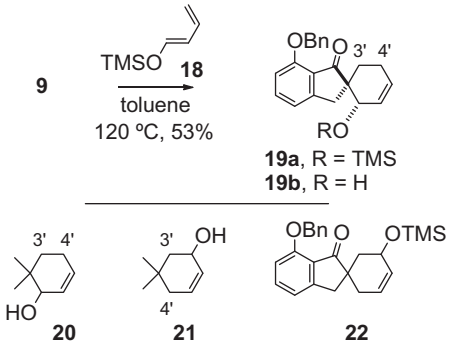


Scheme 3. Reagents and conditions: (i) **13**, MeONa, MeOH, 32%; (ii) $CH_2O_{(aq)}$, 1,4-dioxane, 46%; (iii) cyclopentadiene (**10**), toluene, 120 °C, 37% combined yield (**16**:**17**, 6.1:1).



Scheme 4. Construction of the spiro-fused indanone **19a**.

synthetic route involved the rearrangement of **6** into the indanone **7**.[2a,8] This was accomplished by heating a solvent-free melt of **6** and anhydrous aluminium chloride at 180 °C for 20 min, and then at 200 °C for 30 min, to give 7-hydroxyindanone (**7**) in 75% yield (Scheme 2). The yield of this reaction significantly depended on the reaction time and temperature. For example, the product yield decreased when the reaction time at either temperature was increased. The phenol in **7** was alkylated using benzyl bromide in the presence of tetrabutylammonium iodide and potassium carbonate in DMF to give the protected indanone **8** in quantitative yield.[2a] Installation of the exocyclic alkene was achieved by treatment of **8** with *para*-formaldehyde and morpholine in glacial acetic acid to give the dienophile **9** in 93% yield.[9,10] We were pleased to discover the cycloaddition reaction between the enone **9** and cyclopentadiene (**10**),[11] conducted in refluxing toluene over 18 h, gave a 1:3.6 mixture of the cycloadducts **11** and **12** in 79% combined yield.

We next set our sights on the construction of the ene-dione **15**, which could be derived from the indanone **8**, and the subsequent [4 + 2]-cycloaddition studies. Our synthesis of **15** began with the preparation of aldehyde **13** from phenylhydrazine and methylglyoxal 1,1-dimethyl acetal.[12,13] Treatment of indanone **8** with sodium methoxide in methanol, followed by the aldehyde **13** gave the enone **14** (Scheme 3). The ketone was then unmasked using aqueous formaldehyde in 1,4-dioxane to give the ene-dione **15**. The structures **14** and **15** were assigned the *Z*-alkene geometry based on the allylic coupling constants measured in the proton NMR spectra (ca. 2.4 Hz).[14] The cycloaddition reaction between the ene-dione **15** and cyclopentadiene (**10**) was conducted in refluxing toluene over 18 h to give a 6.1:1 mixture of the cycloadducts **16** and **17** in 37% combined yield.[15]

Based on the success of these preliminary cycloaddition studies we attempted to employ the enone **14** as the dienophile in a reaction with the diene **10**. Unfortunately, none of the desired cycloadduct was isolated, and only the starting dienophile was recovered. Furthermore, our attempts to employ furan as a diene in cycloaddition reactions using the dienophiles **9** and **15** met with similar frustration.

The success of the cycloaddition reactions using cyclopentadiene (**10**) and the dienophiles **9** and **15**, led us to study the regioselectivity of this reaction using a non-symmetrical diene substrate. For example, we chose to investigate the cycloaddition reaction between the dienophile **15** and the diene **18**, which was prepared from crotonaldehyde and chlorotrimethylsilane using zinc chloride and triethylamine.[16] Unfortunately, only the starting ene-dione **15** was recovered when the reaction was performed in a sealed tube, or under the conditions described earlier. However, we were pleased to discover the cycloaddition reaction between the enone **9** and the diene **18** led exclusively to the adduct **19a** in 53% yield,[17,18] together with 9% recovery of the starting dienophile **9** (Scheme 4). Based on our synthetic strategy (see Scheme 1) the spiro-fused indanone **19a** was formed with the appropriate regiochemistry for elaboration of coleophomone A (**1**).

The structures of the major cycloadducts **12**, **16** and **19a** were determined using either single-crystal X-ray diffraction or 1D, 2D and NOE NMR spectroscopy. For example, on the basis of COSY, HMQC and NOE NMR data, the major adduct **16** was determined to be the *endo* diastereoisomer. This assignment was based on NOE NMR enhancements observed between $H_{7a'}$ and H_{3b}, $H_{2'}$ and the geminal proton $H_{7b'}$ (Fig. 1), and supported by selected proton NMR coupling constants. The minor adduct **17** was tentatively assigned as the *exo* diastereoisomer. In contrast, the major adduct **12** was determined to be the *exo* diastereoisomer based on a single-crystal X-ray structure (Fig. 2).[19] The minor adduct **11** was tentatively assigned as the *endo* diastereoisomer. The differences we observed in the diastereoselectivity of the cycloaddition reactions using the dienophiles **9** and **15** presumably reflects the product stability in the case of *exo*-**12** (from **9**) or the degree of orbital overlap between the diene **10** and dienophile **15**, as in the case of *endo*-**16**. The substitution pattern of the dienophile is known to govern the diastereoselectivity of the reaction.[20]

The adduct **19a** was determined to be the *exo* diastereoisomer, with pseudo-*ortho* regiochemistry, which was consistent with the electron-withdrawing properties of the dienophile and the electron-donating properties of the diene. The regiochemical assignment was based on COSY and HMQC NMR data recorded for **19a**. For example, the strong COSY correlations between all the protons on C-3′ and C-4′ clearly indicated the two methylene groups were adjacent. It is unlikely these correlations would be observed for the regioisomer **22**. Furthermore, selected carbon NMR data reported for the isomeric cyclohexenols **20** and **21** supported our regiochemical assignment.[21] For example, the strong correlation between the chemical shift values reported for the carbons C-3′ and C-4′ in **20** and the corresponding values recorded for the adduct **19a** supported our assignment (Table 1). The relative stereochemical assignment of the adduct **19a**, as the *exo* diastereoisomer, was based on the NOE NMR enhancements observed between $H_{1'}$ and

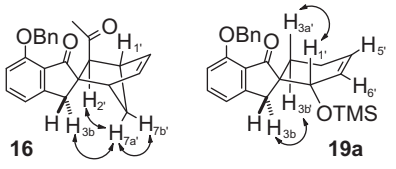


Figure 1. Selected NOE NMR enhancements observed for the cycloadducts **16** and **19a**.

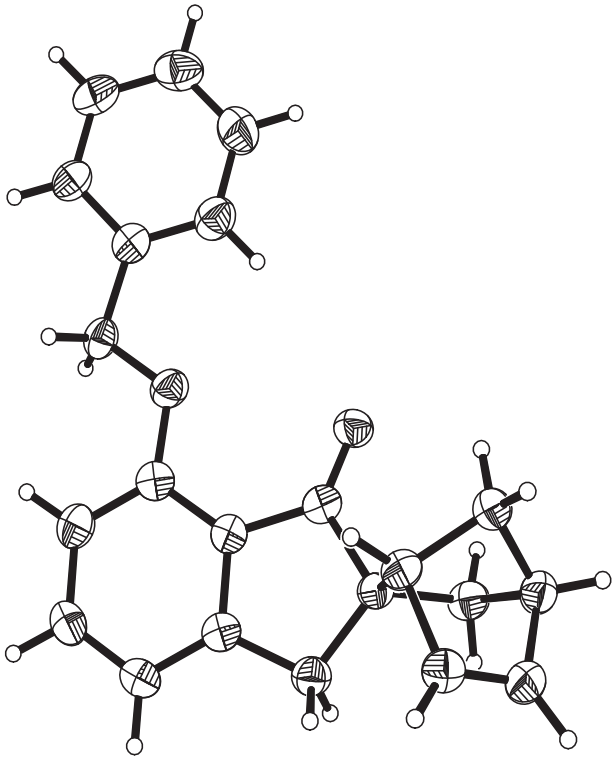


Figure 2. ORTEP representation of the cycloadduct *exo*-**12** at the 50% probability level.

Table 1
Selected carbon NMR chemical shift data for the cyclohexenes **19a**, **20** and **21**[a]

	19a	20	21
C-3′	29.0	32.4	44.8
C-4′	22.8	22.4	38.8

[a] The ^{13}C NMR (25 MHz) data for compounds **20** and **21** were recorded in $CDCl_3$ (see Ref. 21c).

$H_{3a'}$, and between $H_{3b'}$ and H_{3b} (see Fig. 1), and supported by selected proton NMR coupling constants.

In summary, the indanone-based dienophiles **9** and **15** were constructed and successfully employed in [4 + 2]-cycloaddition reactions leading to the spiro-fused indanone structures *exo*-**12**, *endo*-**16** and *exo*-**19a**. The structures of the major adducts *endo*-**16** and *exo*-**19a** were assigned based on COSY, HMQC and NOE NMR data, and that of *exo*-**12** was based on a single-crystal X-ray structure determination. The cycloaddition reactions using the α-methylene indanone **9** preferentially formed the *exo* adducts, for example, **12** and **19a**, while in contrast, the reaction which employed the α-methylene indanone **15** preferentially formed the *endo* adduct, for example, **16**. To the best of our knowledge, the results of these preliminary studies represent the first cycloaddition-based approach to carbocyclic spiro-fused indanones, and have established the precedent for future applications in synthesis. Work is now underway to optimize the reaction conditions, evaluate different methods, and expand this synthetic approach to include other substrates. Furthermore, we plan to exploit the regio- and diastereoselective cycloaddition reaction between **9** and the diene **18**, leading to the adduct **19a**, in the construction of a spirocyclic system, cf. **2**, for elaboration of coleophomone A (**1**). A full account of our cycloaddition approach to spiro-fused indanones, together with our progress towards the natural product, will be disclosed in due course.

Acknowledgements

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15. Purification of the mixture using flash column chromatography gave the major isomer **16** and an inseparable 1:1 mixture of the isomers **16** and **17**. In our hands, the minor isomer **17** could not be separated from the mixture.
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17. A neat sample of the silyl ether **19a**, stored at 5 °C over 40 weeks, was quantitatively converted into the secondary alcohol **19b**.
18. Satisfactory spectroscopic data were recorded for all synthesised compounds reported in this Letter.
Data recorded for the *endo*-adduct **11**: colourless film; R_f = 0.67 (2% Et_2O in toluene); ν_{max} (film/cm^{-1}) 3048, 2951, 2926, 2856, 1700, 1599, 1475, 1275, 736; δ_H (400 MHz, $CDCl_3$) 7.53–7.51 (2H, m, 2 × Ar*H*), 7.45 (1H, dd, *J* 8.0 and 7.5, Ar*H*), 7.39–7.35 (2H, m, 2 × Ar*H*), 7.31–7.27 (1H, m, Ar*H*), 6.97 (1H, dd, *J* 7.5 and 0.6, Ar*H*), 6.81 (1H, d, *J* 8.1, Ar*H*), 6.40 (1H, dd, *J* 5.5 and 3.0, C*H*=CH), 6.07 (1H, dd, *J* 5.5 and 3.0, CH=C*H*), 5.22 (2H, s, PhCH_2O), 3.29 (1H, d, *J* 17.0, C*H*H), 3.16 (1H, d, *J* 17.0, CH*H*), 3.02–3.01 (1H, m, C*H*), 2.60 (1H, dd, *J* 2.5 and 1.5, C*H*), 1.75 (2H, m, CH_2), 1.60–1.58 (1H, m, C*H*H), 1.55–1.52 (1H, m, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.7 (s), 156.8 (s), 154.7 (s), 137.9 (d), 136.6 (s), 135.6 (d), 133.0 (d), 128.6 (d), 127.6 (d), 126.7 (d), 125.6 (s), 118.2 (d), 110.8 (d), 70.0 (t), 55.5 (s), 54.7 (d), 50.2 (t), 44.1 (t), 43.6 (d), 40.0 (t); *m*/*z* (ES) 339.1343 (M^++Na, 100%, $C_{22}H_{20}O_2Na$ requires 339.1361).
Data recorded for the *exo*-adduct **12**: colourless solid; mp 91–92 °C (EtOAc); R_f = 0.77 (2% Et_2O in toluene); ν_{max} (KBr/cm^{-1}) 3067, 2954, 2930, 1701, 1590, 1498, 1298, 1030, 733; δ_H (500 MHz, $CDCl_3$) 7.54–7.52 (2H, m, Ar*H*), 7.43 (1H, dd, *J* 8.1 and 7.6, Ar*H*), 7.40–7.37 (2H, m, 2 × Ar*H*), 7.31–7.27 (1H, m, Ar*H*), 6.92 (1H, dd, *J* 7.5 and 0.7, Ar*H*), 6.79 (1H, d, *J* 8.1, Ar*H*), 6.42 (1H, dd, *J* 5.6 and 3.0, C*H*=CH), 6.23 (1H, dd, *J* 5.6 and 3.0, CH=C*H*), 5.27 (2H, s, PhCH_2O), 3.02 (1H, d, *J* 17.5, C*H*H), 3.00–2.98 (1H, m, C*H*), 2.79–2.78 (1H, m, C*H*), 2.78 (1H, d, *J* 17.5, CH*H*), 2.40 (1H, br d, *J* 8.6, C*H*H), 2.34 (1H, dd, *J* 11.5 and 3.6, CHC*H*HCH), 1.37

(1H, dq, *J* 8.4 and 1.5, CH*H*), 1.15 (1H, dd, *J* 11.5 and 2.9, CHCH*H*CH); δ_C (125 MHz, $CDCl_3$) 208.0 (s), 157.0 (s), 155.1 (s), 140.7 (d), 136.6 (s), 135.8 (d), 135.6 (d), 128.6 (d), 127.7 (d), 126.7 (d), 125.1 (s), 118.1 (d), 110.6 (d), 70.1 (t), 55.7 (s), 51.3 (d), 47.0 (t), 43.4 (d), 41.5 (t), 41.1 (t); *m*/*z* (ES) 339.1353 (M^++Na, 100%, $C_{22}H_{20}O_2Na$ requires 339.1361).

Data recorded for the *endo*-adduct **16**: brown solid; mp 96–98 °C (EtOAc); R_f = 0.37 (20% EtOAc in pentane); ν_{max} (KBr/cm^{-1}) 3064, 2960, 2924, 2853, 1700, 1600, 1456, 1261, 1096, 802; δ_H (500 MHz, $CDCl_3$) 7.55 (2H, m, 2 × Ar*H*), 7.47 (1H, t, *J* 7.8, Ar*H*), 7.42–7.39 (2H, m, 2 × Ar*H*), 7.33–7.30 (1H, m, Ar*H*), 6.93 (1H, dd, *J* 7.5 and 0.6, Ar*H*), 6.83 (1H, d, *J* 8.2, Ar*H*), 6.60 (1H, dd, *J* 5.5 and 3.0, C*H*=CH), 6.25 (1H, dd, *J* 5.5 and 3.0, CH=C*H*), 5.28 (2H, s, OCH_2Ph), 3.77 (1H, d, *J* 2.9, C*H*COCH$_3$), 3.15 (1H, d, *J* 1.0, C*H*), 2.83–2.82 (3H, m, C(4°)CH_2 and C*H*), 2.30–2.28 (1H, m, C*H*H), 1.91 (3H, s, CH_3), 1.33 (1H, dt, *J* 8.7 and 1.6, CH*H*); δ_C (125 MHz, $CDCl_3$) 209.3, 205.4, 157.1, 155.1, 139.8, 136.3, 136.2, 135.3, 128.5, 127.7, 126.5, 118.0, 110.6, 69.9, 62.0, 53.0, 46.4, 45.1, 36.2, 31.6; *m*/*z* (ES) 381.1487 (M^++Na, 100%, $C_{24}H_{22}O_3Na$ requires 381.1467).

Data recorded for the *exo*-adduct **19a**: colourless film; R_f = 0.68 (50% EtOAc in petroleum ether); ν_{max} (film/cm^{-1}) 3048, 3024, 2968, 2927, 2839, 1733, 1699, 1600, 1227, 1069, 737; δ_H (500 MHz, $CDCl_3$) 7.53–7.51 (2H, m, 2 × Ar*H*), 7.43 (1H, t, *J* 7.8, Ar*H*), 7.39–7.35 (2H, m, 2 × Ar*H*), 7.30–7.27 (1H, m, Ar*H*), 6.97 (1H, br dt, *J* 7.5 and 0.7, Ar*H*), 6.74 (1H, d, *J* 8.1, Ar*H*), 5.74–5.72 (1H, m, CH(OH)C*H*=CH), 5.55–5.52 (1H, m, CH(OH)CH=C*H*), 5.26 (2H, d, *J* 5.1, PhCH_2O), 4.65–4.62 (1H, m, C*H*OSi(CH$_3$)$_3$), 3.34 (1H, d, *J* 17.2, C*H*H), 2.73 (1H, d, *J* 17.2, CH*H*), 2.17–2.13 (2H, m, C(4°)CH_2CH_2), 2.04–1.98 (1H, m, C(4°)C*H*HCH$_2$), 1.59–1.55 (1H, m, C(4°)CH*H*CH$_2$), −0.10 (9H, s, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 208.1 (s), 157.6 (s), 156.9 (s), 136.9 (s), 136.2 (d), 132.2 (d), 128.7 (d), 127.7 (d), 127.4 (d), 126.7 (d), 125.8 (s), 118.5 (d), 110.3 (d), 71.0 (d), 70.0 (t), 54.3 (s), 32.3 (t), 29.0 (t), 22.8 (t), 0.0 (q).

Data recorded for the alcohol **19b**: pale yellow solid; mp = 193–195 °C (EtOAc); R_f = 0.29 (80% EtOAc in petroleum ether); ν_{max} (KBr/cm^{-1}) 3469, 3032, 2952, 2920, 2851, 1677, 1597, 1480, 1270, 1056, 779; δ_H (400 MHz, $CDCl_3$) 7.55–7.52 (2H, m, Ar*H*), 7.48 (1H, t, *J* 7.8, Ar*H*), 7.41–7.37 (2H, m, 2 × Ar*H*), 7.32–7.30 (1H, m, Ar*H*), 7.01 (1H, dd, *J* 8.2 and 0.6, Ar*H*), 6.79 (1H, d, *J* 8.2, Ar*H*), 5.81–5.76 (1H, m, C*H*=CH), 5.81 (1H, dq, *J* 10.1 and 2.0, CH=C*H*), 5.24 (2H, s, PhCH_2O), 4.77–4.76 (1H, m, C*H*OH), 3.33 (1H, d, *J* 17.3, C*H*H), 2.82 (1H, d, *J* 17.3, CH*H*), 2.21–2.17 (2H, m, C(4°)CH_2CH_2), 2.01–1.93 (1H, m, C(4°)C*H*HCH$_2$), 1.59–1.55 (1H, m, C(4°)CH*H*CH$_2$); δ_C (100 MHz, $CDCl_3$) 207.9 (s), 157.1 (s), 156.9 (s), 136.6 (s), 136.5 (d), 130.8 (d), 118.7 (d), 110.4 (d), 70.1 (t), 70.0 (d), 54.2 (s), 31.6 (t), 29.1 (t), 22.9 (t); *m*/*z* (ES) 343.1308 (M^++Na, 100%, $C_{21}H_{20}O_3Na$ requires 343.1310).

19. Crystal data for **12**: $C_{22}H_{20}O_2$, M = 316.4, orthorhombic, a = 5.577(2), b = 15.715(7), c = 18.402(10) Å, U = 1612.8(2) Å^3, T = 150(2) K, Mo-Kα radiation, λ = 0.71073 Å, space group $P2_12_12_1$ (no. 19), Z = 4, F(0 0 0) = 672, D_x = 1.303 g cm^{-3}, μ = 0.082 mm^{-1}, measured/independent reflections: 12,324/2734, R_{int} = 0.084, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.045 for 2319 data with $F_o > 4\sigma(F_o)$, 217 parameters, ωR_2 = 0.123 (all data), GoF = 1.13, $\Delta\rho_{min,max}$ = −0.39/0.37 e Å^{-3}. The racemic sample is a spontaneously resolved conglomerate comprising individual crystals that are enantiopure (*R*,*R*,*R*) and (*S*,*S*,*S*). Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 797032. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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