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Stereoselective total syntheses of (±)-1,14-herbertenediol and (±)-tochuinyl acetate and facile total syntheses of (±)-α-herbertenol, (±)-β-herbertenol and (±)-1,4-cuparenediol

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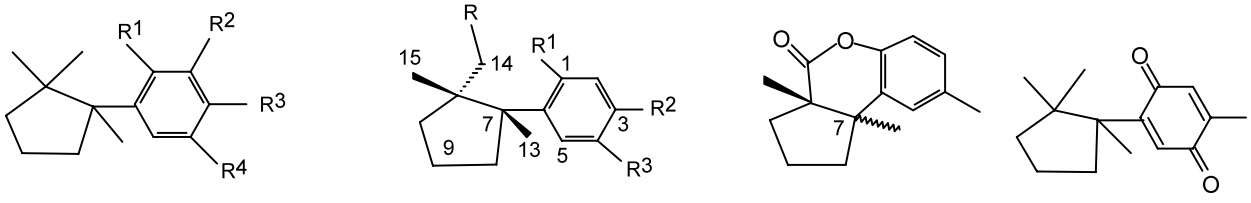
Abstract—Stereoselective total syntheses of (±)-1,14-herbertenediol (**7**) and (±)-tochuinyl acetate (**10**) and facile total syntheses of (±)-α-herbertenol (**2**), (±)-β-herbertenol (**3**) and (±)-1,4-cuparenediol (**8**) have been successfully accomplished involving intramolecular cyclisation of 3-aryl-3-methyl-6-bromohexanoates and in situ methylation of the resulting cyclopentanecarboxylates as the key reactions.

Herbertanes and cuparanes possessing sterically crowded cyclopentane moieties belong to an expanding family of sesquiterpenes and have become popular synthetic targets in recent years as some members exhibit interesting biological activities. The isolation of the first members of the herbertane family herbertene (**1**), α-herbertenol (**2**), β-herbertenol (**3**), herbertenediol (**4**), and herbertenolide (**5**) (Fig. 1) from the liverwort *Herberta adunca* was reported[1] earlier by Matsuo and co-workers. Recently, Asakawa and co-workers reported[2,3] the isolation of seven new herbertanes and two new cuparanes from Japanese liverworts. Many of the sesquiterpenes isolated from liverworts, particularly the sesquiterpene phenols, show a wide spectrum of biological properties which include[1,4] potent antifungal, neurotrophic and anti-lipid peroxidation activities. 1,14-Herbertenediol (**7**),[2] 1,4-cuparenediol (**8**)[3] and cuparene-1,4-quinone (**9**)[3] (Fig. 1) are a few examples of recently isolated sesquiterpenes from liverworts with novel structural features. The total synthesis of naturally occurring sesquiterpenes containing the 1-aryl-1,2,2-trimethylcyclopentane ring system has been an active area of research in recent times and current interest[5] in phenolic sesquiterpenes is reflected in the



1, $R^1 = R^2 = R^3 = H$, $R^4 = Me$

2, $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = Me$

3, $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = Me$

4, $R^1 = R^2 = OH$, $R^3 = H$, $R^4 = Me$

8, $R^1 = R^4 = OH$, $R^2 = H$, $R^3 = Me$

7, $R = R^1 = OH$, $R^2 = H$, $R^3 = Me$

10, $R = OAc$, $R^1 = R^3 = H$, $R^2 = Me$

5, α - Me at C-7

6, β - Me at C-7

9

Figure 1.

Keywords: terpenes; phenols; conjugate addition; cyclisation; alkylation.

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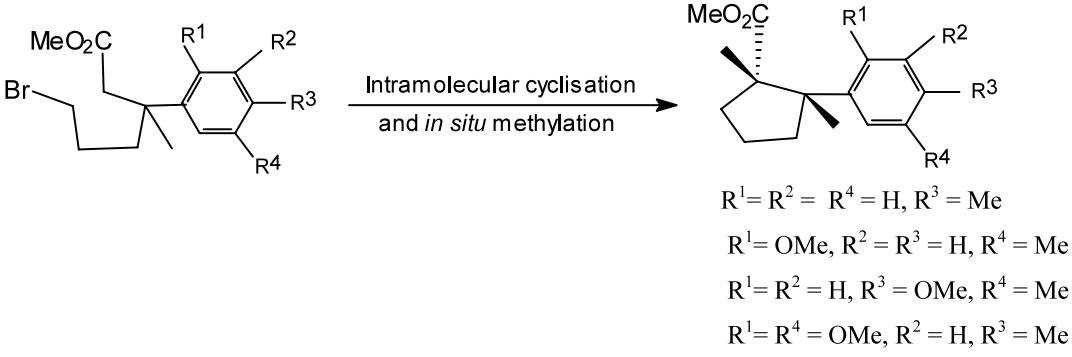
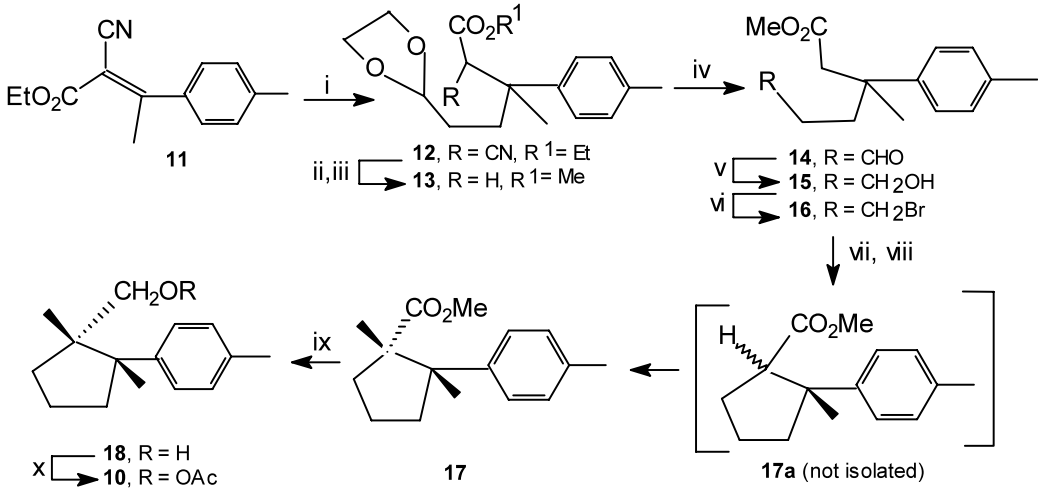
number of diverse synthetic approaches to these compounds. The synthesis of these sesquiterpenes is associated with the difficulty of the generation of the two adjacent quaternary carbon atoms at C-1 and C-2 on the cyclopentane ring and an appropriately substituted, often highly substituted, aromatic ring at C-1. We have recently developed a very useful and convenient general method for the synthesis of herbertane and cuparane sesquiterpenes from easily accessible 3,3-disubstituted-6-bromohexanoates, employing an intramolecular anionic cyclisation strategy to generate the vicinally substituted cyclopentanes related to the natural products. We envisaged that intramolecular cyclisation of 3-aryl-3-methyl-6-bromohexanoates in the presence of base and in situ methylation of the resulting cyclopentanecarboxylates from the less hindered face would generate stereoselectively, in one step, 1,1,2,2-tetrasubstitutedcyclopentanes related to naturally occurring herbertanes and cuparanes as shown in Scheme 1. Based on this approach, we have successfully accomplished a new total synthesis of the bioactive phenolic herbertanes **2** and **3** and the first total synthesis of the cuparane sesquiterpenes **8** and **9**. Highly stereoselective total syntheses of 1,14-herbertenediol (**7**), via 11-*epi*-herbertenolide (**6**), and the cuparane-type sesquiterpene tochuinyl acetate (**10**),[6] a marine natural product, have also been achieved during the present studies. The sesquiterpenes **7** and **10** possess two vicinal stereogenic quaternary carbon atoms on a cyclopentane ring and have recently attracted the attention[7] of many synthetic chemists.

A stereocontrolled total synthesis of tochuinyl acetate (**10**) was initially undertaken. The marine sesquiterpene **10** was isolated[6] from the dendronotid nudibranch *Tochuina tetraquetra* and also from its feed, the soft coral *Gersemia rubiformis*. As mentioned before, the presence of a sterically congested cyclopentane ring with two vicinal stereogenic quaternary centres makes the acetate **10** an interesting synthetic target. The first synthesis of (±)-**10** was accomplished by Ishibashi et al.[8] using a thiochromane approach, and later Taber and co-workers[9] synthesised (±)-**10** involving rhodium catalysed intramolecular C–H insertion of a diazo ketone as a key step. Very recently, Srikrishna and co-workers[7] achieved the synthesis of (±)-**10**, employing a ring-closing metathesis reaction based methodology.



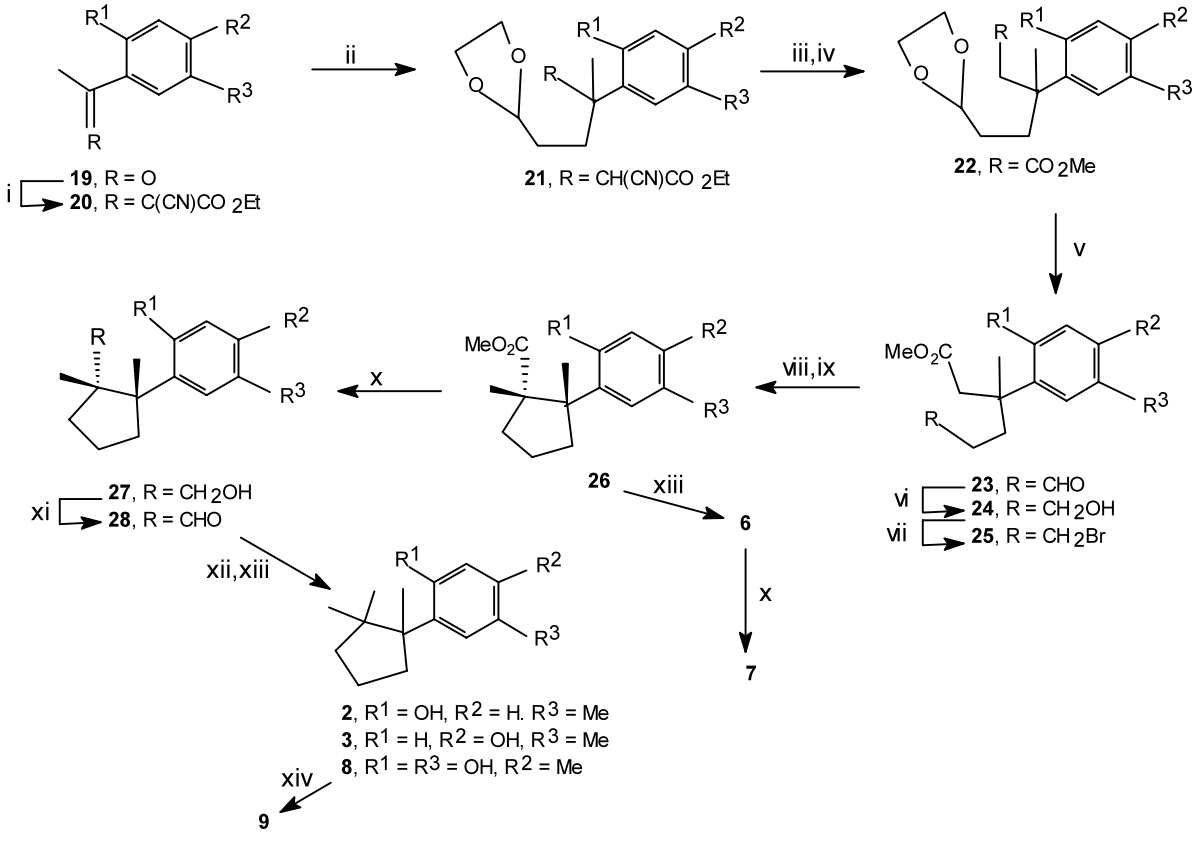
Scheme 1.

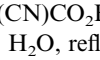


Scheme 2. *Reagents and conditions*: (i) $\left[\begin{smallmatrix}O\\O\end{smallmatrix}\right\rangle CHCH_2CH_2MgBr$, CuBr·$Me_2S$, THF, Et_2O, 0–20°C; (ii) KOH, $HOCH_2CH_2OH$, H_2O, reflux, AcOH, 0°C; (iii) CH_2N_2, Et_2O, 0°C; (iv) AcOH–H_2O (4:1), 25–60°C; (v) $NaBH_4$, MeOH, 0–25°C; (vi) PBr_3, C_6H_6, 0–70°C; (vii) LDA (1.2 equiv.), THF, HMPA (1.5 equiv.), −70°C; (viii) LDA (1.6 equiv.), HMPA (2 equiv.), THF, 0°C, MeI, 0°C; (ix) LAH, THF, reflux; (x) Ac_2O, C_5H_5N, 25°C.

Our synthesis of (±)-tochuinyl acetate **10** is outlined in Scheme 2. The first quaternary carbon atom was created through conjugate addition to the unsaturated cyanoester **11**. Thus, conjugate addition of 3,3-ethylenedioxypropylmagnesium bromide[10] to the unsaturated cyanoester **11** in the presence of $CuBr{\cdot}S(CH_3)_2$ provided **12**[11] (58%) which on hydrolysis, decarboxylation and esterification afforded the ester **13** in 75% yield. Deacetalisation of **13** followed by reduction of the resulting aldehyde **14** with $NaBH_4$ afforded the primary alcohol **15** (83%) which was treated with PBr_3 to give the bromoester **16** in 74% yield. The bromoester **16** was converted into the cyclopentanecarboxylate **17**[12] (85%) in a one pot process involving an intramolecular cyclisation of **16** by treatment with LDA (1.2 equiv.) in THF and HMPA at −70°C followed by alkylation with MeI at 0°C in the presence of LDA (1.6 equiv.) and HMPA (2 equiv.), without isolating the initial cyclised product **17a**. The second quaternary carbon atom was thus generated very efficiently and in a stereoselective manner, highlighting the potential of the present method. The high stereoselectivity observed in the transformation of **16** into **17** is due to methylation taking place from the less hindered side[7] of the intermediate enolate of the ester **17a**. In the ^1H NMR spectrum of **17**, the ester methyl signal appeared at δ 3.25 ppm, indicating shielding of the methoxycarbonyl group by the vicinal *cis* aryl group. The stereostructure **17** of the ester, as shown in Scheme 2, was further confirmed by conversion of **17**, which is suitably functionalised into (±)-tochuinyl acetate (**10**). Thus, reduction of **17** with $LiAlH_4$ followed by acetylation of the resulting alcohol **18** furnished (±)-**10** in 72% overall yield. The spectral data of synthetic **10** were identical with those of the natural product.

We have further explored the possibility of application of the present method to the total synthesis of the sesquiterpene phenols α-herbertenol (**2**), β-herbertenol (**3**), herbertenediol (**7**), and cuparenediol (**8**) which were isolated from liverworts. The present synthesis of the phenolic sesquiterpenes is outlined in Scheme 3 The acetophenones **19a**, **19b** and **19c**[13] were condensed with ethyl cyanoacetate to provide the unsaturated cyanoesters **20a** (75%), **20b** (73%) and **20c** (75%), respectively. Conjugate addition of 3,3-ethylenedioxypropylmagnesium bromide to **20a–c** in the presence of $CuBr{\cdot}S(CH_3)_2$ afforded **21a** (58%), **21b** (60%) and **21c** (58%) which on hydrolysis, decarboxylation and esterification furnished the methyl esters **22a** (75%), **22b** (77%), and **22c** (74%), respectively. Deacetalisation of **22a** followed by reduction of the resulting aldehyde **23a** with $NaBH_4$



Scheme 3. 19a–28a: R^1 = OMe, R^2 = H, R^3 = Me; **19b–28b**: R^1 = H, R^2 = OMe, R^3 = Me; **19c–28c**: $R^1 = R^3$ = OMe, R^2 = Me. *Reagents and conditions*: (i) $CH_2C(CN)CO_2Et$, NH_4OAc, AcOH, C_6H_6, reflux; (ii)  , $CuBr{\cdot}Me_2S$, THF, Et_2O, 0–20°C; (iii) KOH, $HOCH_2CH_2OH$, H_2O, reflux, AcOH, 0°C; (iv) CH_2N_2, Et_2O, 0°C; (v) AcOH–H_2O (4:1), 25–60°C; (vi) $NaBH_4$, MeOH, 0–25°C; (vii) PBr_3, C_6H_6, 0–70°C; (viii) LDA (1.2 equiv.), THF, HMPA (1.5 equiv.), −70°C; (ix) LDA (1.6 equiv.), HMPA (2 equiv.), THF, 0°C, MeI, 0°C; (x) LAH, THF, reflux; (xi) PCC, NaOAc, CH_2Cl_2, 25°C; (xii) N_2H_4, $N_2H_4{\cdot}2HCl$, $(HOCH_2CH_2)_2O$, 125°C; KOH, 210°C; (xiii) BBr_3, CH_2Cl_2, −70 to 20°C; (xiv) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O, 25°C.

afforded the primary alcohol **24a** (82%) which was converted into the bromoester **25a** (72%) with PBr_3. The esters **22b** and **22c** were similarly converted into the bromoesters **25b** (62%) and **25c** (62%), respectively. As described earlier for **17**, the transformation of the bromoester **25a** into the cyclopentanecarboxylate **26a** was accomplished in 83% yield in a one pot process employing an intramolecular cyclisation of **25a** using LDA as the base followed by in situ methylation of the resulting product. Intramolecular cyclisation and in situ methylation of the esters **25b** and **25c** were similarly carried out to provide the esters **26b** (85%) and **26c** (85%), respectively. As expected, very high diastereoselectivity was observed in the above transformations. In the ^1H NMR spectra of **26a–c**, upfield singlets, characteristic[14] of the methyl group *cis* to the aromatic ring in cuparanes, were absent but the ester methyl signals appeared at δ 3.18, 3.28 and 3.26 ppm, respectively. The upfield shifts of the ester methyl signals indicated shielding of the methoxycarbonyl groups by the vicinal *cis* aryl groups, establishing the stereochemistry of these intermediates as shown in Scheme 3.

Reduction of the esters **26a-c** with $LiAlH_4$ afforded the primary alcohols **27a**[12] (88%), **27b** (90%) and **27c** (85%) which on oxidation with pyridinium chlorochromate provided the aldehydes **28a** (84%), **28b**[12] (85%) and **28c** (84%), respectively. Huang–Minlon reduction of **28a** followed by demethylation with BBr_3 afforded (±)-α-herbertenol (**2**) (71%). Similarly, Huang–Minlon reduction of **28b** and **28c** and subsequent demethylation of the resulting products with BBr_3 furnished β-herbertenol (**3**) (71%) and (±)-1,4-cuparenediol (**8**)[12] (70%), respectively. Oxidation of **8** with ceric ammonium nitrate afforded (±)-cuparene-1,4-quinone (**9**)[12] in 88% yield.

The ester **26a** was smoothly converted into the lactone 11-*epi*-herbertenolide (**6**) (78%) by treatment with BBr_3. Reduction of **6** with $LiAlH_4$ finally yielded 1,14-herbertenediol (**7**)[12] in 91% yield. The identities of our synthetic compounds **2**, **3**, **8**, **9** and **7** were secured through comparison of ^1H and ^{13}C NMR data with those of authentic compounds.

In conclusion, we have developed a convenient and useful general method for the synthesis of herbertane and cuparane sesquiterpenes based on intramolecular cyclisation of 3-aryl-3-methyl-6-bromohexanoates and in situ methylation of the resulting cyclopentanecarboxylates. Stereocontrolled total syntheses of (±)-1,14-herbertenediol and (±)-tochuinyl acetate and facile total syntheses of (±)-α-herbertenol, (±)-β-herbertenol and (±)-1,4-cuparenediol have been achieved by the application of the present method.

Acknowledgements

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11. Satisfactory spectroscopic and microanalytical data were obtained for all new compounds.
12. Selected spectral data for the ester **17**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H), 1.40 (s, 3H), 1.56–2.00 (m, 4H), 2.27–2.37 (m, 1H), 2.28 (s, 3H), 2.52–2.60 (m, 1H), 3.25 (s, 3H), 7.05 (d, 2H, $J=8.4$ Hz), 7.17 (d, 2H, $J=8.4$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.3, 20.7, 21.1, 24.2, 35.8, 37.9, 50.9, 51.4, 56.6, 126.2, 126.2, 128.3, 128.3, 135.3, 143.4, 176.9. For the alcohol **27a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 1.41 (s, 3H), 1.31–2.48 (m, 7H), 2.27 (s, 3H), 3.12 (bs, 2H), 3.78 (s, 3H), 6.79 (d, 1H, $J=8.1$ Hz), 7.00 (dd, 1H, $J=8.1$, 1.9 Hz), 7.08 (d, 1H, $J=1.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 20.9, 21.2, 24.0, 37.1, 41.9, 48.9, 50.3, 55.2, 70.4, 112.0, 127.7, 129.3, 129.8, 135.1, 156.2. For the aldehyde **28b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (s, 3H), 1.29 (s, 3H), 1.52–1.60 (m, 1H), 1.75–2.39 (m, 5H), 2.20 (s, 3H), 3.78 (s, 3H), 6.73 (d, 1H, $J=9$ Hz), 7.10 (d, 1H, $J=9$ Hz), 7.11 (s, 1H), 9.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.4, 16.5, 20.7, 24.6, 33.1, 37.7, 49.7, 55.1, 58.5, 109.4, 124.7, 126.0, 128.9, 135.8, 156.1, 206.4. For 1,4-cuparenediol **8**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.76 (s, 3H), 1.16 (s, 3H), 1.38 (s, 3H), 1.47–1.77 (m, 5H), 2.15 (s, 3H), 2.49–2.53 (m, 1H), 4.41 (bs, 1H), 4.49 (bs, 1H), 6.46 (s, 1H), 6.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 20.2, 22.9, 25.4, 26.9, 39.4, 41.1, 44.7, 50.8, 116.2, 119.1, 121.9, 132.0, 146.8, 148.1. For cuparene-1,4-quinone **9**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74 (s, 3H), 1.12 (s, 3H), 1.29 (s, 3H), 1.51–1.76 (m, 5H), 2.01 (d, 3H, $J=1.5$ Hz), 2.20–2.29 (m, 1H), 6.51 (q, 1H, $J=1.5$ Hz), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.8, 19.8, 22.9, 25.2, 27.8, 38.5, 41.5, 44.0, 51.3, 133.9, 135.5, 143.6, 155.0, 188.2, 188.6. For 1,14-herbertenediol **7**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (s, 3H), 1.55 (s, 3H), 1.18–1.97 (m, 6H), 2.27 (s, 3H), 2.42–2.47 (m, 1H), 3.26, 3.34 (2×d, 2H, $J=11.1$ Hz), 6.73 (d, 1H, $J=7.8$ Hz), 6.91 (dd, 1H, $J=7.8$, 1.5 Hz), 6.96 (d, 1H, $J=1.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 20.9, 21.1, 23.9, 35.9, 42.3, 48.9, 50.9, 70.7, 117.9, 128.0, 129.2, 129.8, 132.9, 153.1.
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