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Rapid entry to functionally rich bicyclo[4.1.0]heptenone systems†

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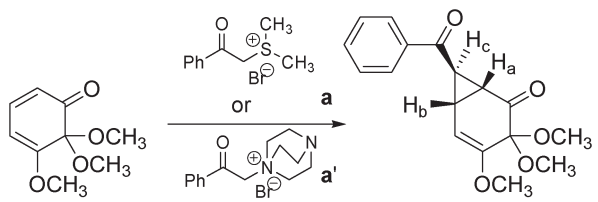
A facile process for the synthesis of highly substituted bicyclo[4.1.0]heptenones *via* Corey–Chaykovsky reaction of quinone monoketals is presented. The obtained products were employed to functionalize 3-position of indoles providing compounds which might have potential use in medicinal chemistry.

Bicyclo[4.1.0]heptane systems were found to have distinctive biological functions.[1a,b] Recently, it was demonstrated that polyhydroxylated bicyclo[4.1.0]heptane products possess α-galactosidase inhibitory activity.[1c] On the other hand, bicyclo[4.1.0]heptane-7-carboxylic amide derivatives were used as food flavor substances.[2a] Moreover, suitably substituted bicyclo[4.1.0]heptan-4-one derivatives were synthesised as novel odorant substances.[2b] In addition, owing to their unique steric and electronic properties, the cyclopropyl ring is present in a large number of pharmaceuticals and also employed as a replacement of the alkene moiety to avoid metabolic liability.[3] Besides, synthesis of medium sized rings *via* the ring opening of the cyclopropane (due to its latent reactivity) of the fused bicyclic systems was successfully applied in the synthesis of natural products.[4] Therefore, based on our interest and inspired by the literature reports on the usefulness of these products, we decided to pursue a general and facile route for the synthesis of functionally rich bicyclo[4.1.0]heptenone systems and envisaged these products as precursors to a variety of compounds with potential applications. Among the reported methodologies for the synthesis of cyclopropane derivatives, sulfur ylide mediated cyclopropanation of conjugated double bond has gained prominent position.[5] During the course of studies involving masked *o*-benzoquinones (MOBs), we have earlier developed a simple and efficient synthesis of highly substituted isoindolines[6b] and in subsequent studies, we further demonstrated that nitrile oxide cycloaddition products of MOB can be transformed to highly substituted benzisoxazoles or rearranged to novel isoxazoline derivatives.[6a] These results cast insight into the new aspects of MOB chemistry in utilizing them as excellent partners in other than Diels–Alder reactions.[6c] To this end, we were convinced that these benzoquinone monoketals as the substrates would enable us to achieve our goal in obtaining functionally rich bicyclo[4.1.0]heptenone derivatives. To the best of our knowledge up until now there are no reports on reaction of stabilized sulfonium ylides (S-ylides) with benzoquinone monoketals.[6d] Herein, we present the results of our preliminary investigation on these reactions.

At the outset, readily available MOB **1**[7] (prepared by oxidation of 2,3-dimethoxyphenol with diacetoxyiodobenzene in methanol) on treating with 1.2 equiv. of dimethylphenacylsulfonium bromide (**a**)[8]‡ in the presence of 2.5 equiv. of K_2CO_3 in acetonitrile at room temperature provided the required bicyclo[4.1.0]heptenone system in 91% isolated yield (Table 1, entry 1). The structure of compound **1a** was confirmed based on ^1H, ^{13}C NMR, DEPT and HRMS analyses. The stereochemistry of the substituents was assigned

Table 1 Synthesis of bicyclo[4.1.0]heptenone **1a** *via* cyclopropanation of MOB **1** with S-ylide **a** or N-ylide **a′**



Entry[a]	Ylide source	Condition	Time/Yield (%)
1	**a**	K_2CO_3, CH_3CN, rt	12 h/91%
2	**a′**	K_2CO_3, CH_3CN, rt	24 h/—[b]
3	**a′**	K_2CO_3, CH_3CN, 80 °C	12 h/89%

[a] Reaction was conducted on 0.75 mmol of MOB **1**, 0.9 mmol of S-/N-ylide and 1.9 mmol of K_2CO_3 in 3 mL of acetonitrile. [b] No reaction.

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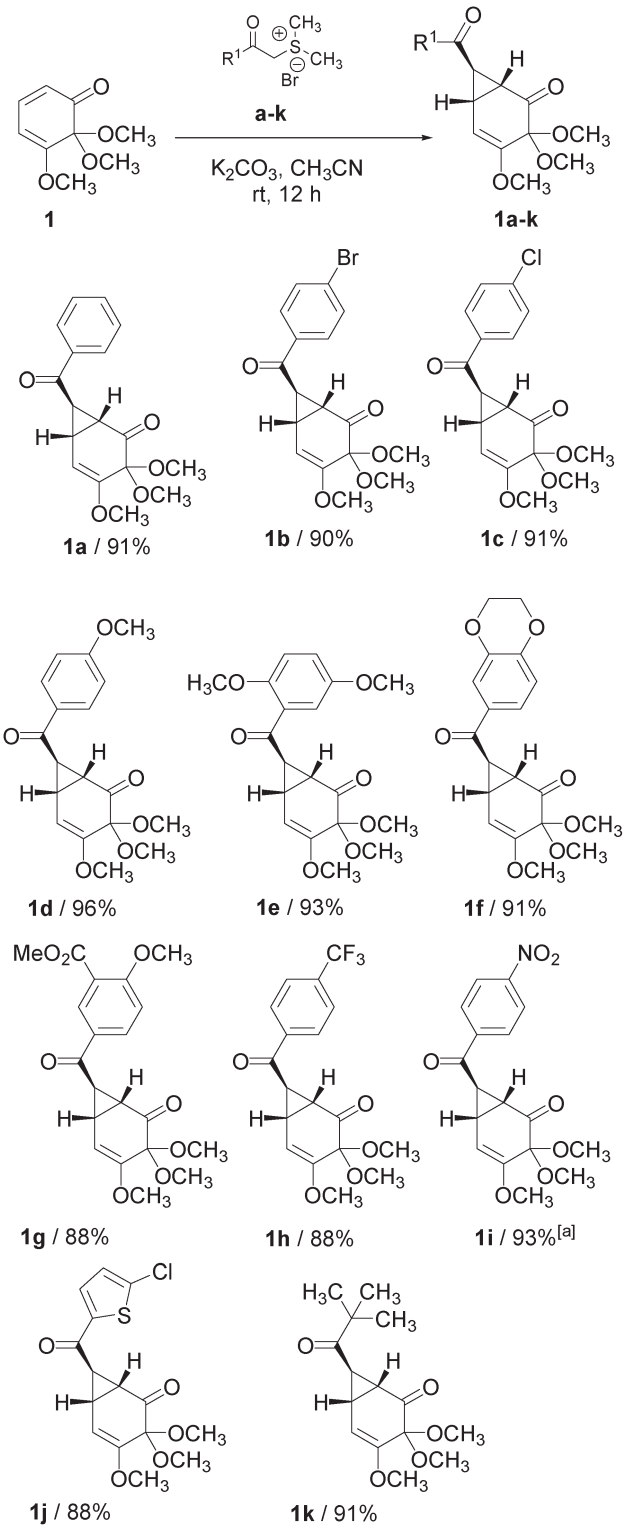
based on the coupling constants of protons on the cyclopropane ring and is in accord with the literature precedents.[9] Of late, nitrogen ylides (N-ylides) are being effectively utilized for the cyclopropanation reaction.[10] Consequently, we were interested to test the feasibility of exploiting the N-ylides as cyclopropanating agents in our study. Thus, *in situ* generated N-ylide from **a′** required reflux temperature to provide the identical product **1a** on reaction with MOB **1** (Table 1, entry 3). Due to this marked difference in the reactivity of S-ylide *vs.* N-ylide with MOB **1**, all our subsequent reactions were carried-out with S-ylides.

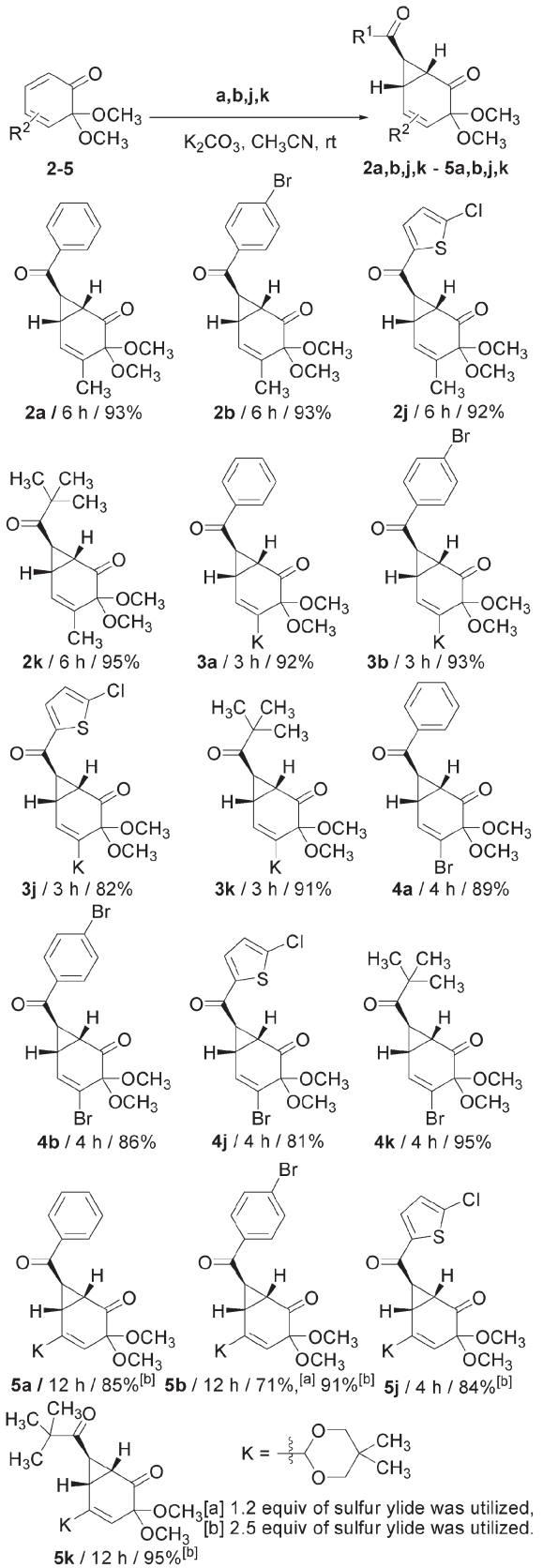
Encouraged by the above successful result, various stabilized S-ylide precursors '**b–k**' were reacted with MOB **1** in the presence of K_2CO_3 in acetonitrile. To our delight, the reaction is compatible with all the stabilized S-ylides (having electron-withdrawing and electron-donating groups on the phenyl residues of the S-ylides, heteroaromatic and aliphatic S-ylides) employed providing the desired bicyclo[4.1.0]heptenone derivatives in high to excellent isolated yields (Scheme 1). Despite the fact that most of the reactions took place at room temperature, S-ylide generated from its precursor '**i**' needed 60 °C to afford the desired bicyclo[4.1.0]-heptenone **1i**, indicating that the electronic factors strongly influence the reactivity of sulfonium ylides. Interestingly, compound **1e** was found to be unstable leading to intractable mixture of products on long standing at room temperature, nevertheless could be stored at 0 °C for days without appreciable decomposition.

To extend the scope of this methodology, MOBs **2–4** were chosen to react with selected set of stabilized S-ylides generated from precursors '**a**, **b**, **j** and **k**'. As demonstrated in Scheme 2, cyclopropanation of MOBs having substituents at 5-position proved to be general approach for the synthesis of these bicyclic derivatives. Subsequently we were interested to probe the reaction of S-ylides with 4-subsituted MOB **5**. Reaction of *in situ* generated S-ylide from '**b**' with MOB **5** did not yield any desired product **5b**, instead furnished cyclopropane **6**[11–13] in high yield at 60 °C (Scheme 3) along with dimer **7** (Scheme 4) and unreacted MOB **5**. Initially, we presumed the poor reactivity of MOB **5** to the steric hindrance by the ketal functionality near to the reactive centre. However, after closer analysis, we found that complete consumption of S-ylide leading to the formation of cyclopropane **6**[12] was the actual reason for the failure of above reaction. We believe that the presence of residual methanol (from the MOB preparation step) in the reaction mixture of MOB **5** and sulfonium bromide '**b**' led to the formation of cyclopropane **6** (Scheme 3). Nevertheless, when methanol free fractions of MOB **5** were treated with the *in situ* generated sulfur ylides obtained from '**b**', desired product was formed albeit with moderate yield (71%) along with dimer **7** (13%, Scheme 4). To circumvent the MOB dimerization problem and to improve the yields of the corresponding bicyclic compounds, excess (2.5 equiv.) of sulfur ylides were utilized in the reaction. As expected, the corresponding products **5a**, **5b**, **5j** and **5k** were obtained in high yields (Scheme 2).

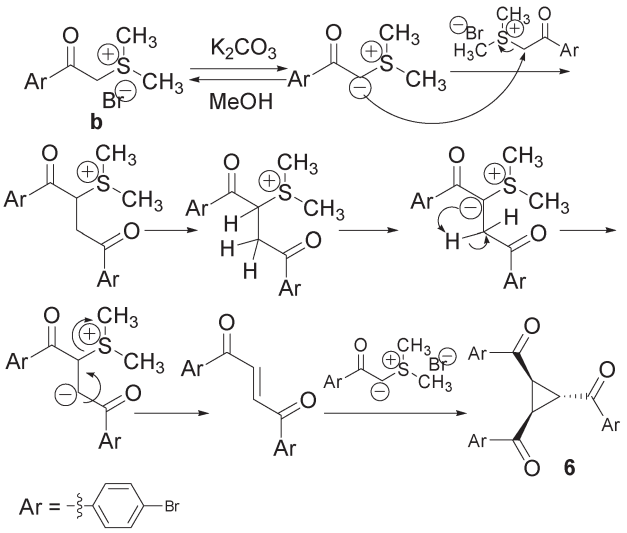
In a separate experiment, sulfonium bromide '**b**' when heated at 60 °C in 10% CH_3OH in CH_3CN as reaction medium in the presence of K_2CO_3 for 8 h furnished triaroylcyclopropane **6** in 90% yield. However, no such product formation occurred when the same reaction was repeated in acetonitrile as the only solvent, further indicating that presence of protic solvent is necessary for such a reaction to take place.[12]



Scheme 1 Synthesis of bicyclo[4.1.0]heptenone derivatives **1a–1k**.



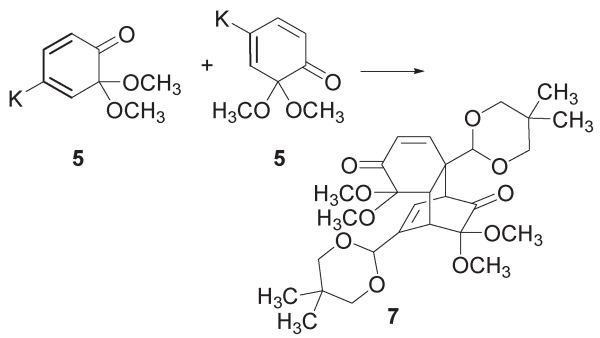
Scheme 2 Synthesis of bicyclo[4.1.0]heptenone derivatives **2a,b,j,k**–**5a,b,j,k**.



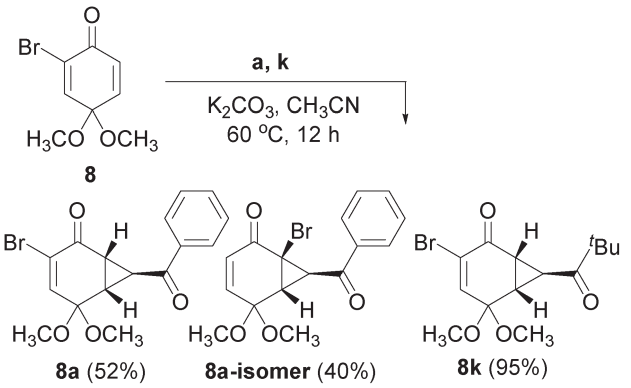
Scheme 3 A plausible mechanism for the formation of triaroylcyclopropane derivative **6** from sulfonium bromide **b**.

In an effort to widen the scope of the Corey–Chaykovsky reaction, the cyclopropanation of *p*-benzoquinone monoketal (masked *p*-benzoquinone, MPB) **8** was performed. MPB **8** underwent facile cyclopropanation with S-ylide generated from '**a**' providing two isomers, and major isomer **8a** is obtained by the reaction of S-ylide with the less substituted double bond (Scheme 5); on the other hand, S-ylide generated from '**k**' gave exclusively bicyclo[4.1.0]heptenone **8k** (Scheme 5). As of now it is unclear why S-ylide generated from '**a**' provided mixture of isomers. Nevertheless, MPBs can also be conveniently utilized for the synthesis of differently substituted bicyclo[4.1.0]heptenone systems.

Our next objective was to develop procedures to further functionalize the obtained bicyclo[4.1.0]heptenone adducts. Indoles are drug-like scaffolds and numerous synthetic indoles have been submitted to pharmacological investigation.[14] Further, quite a few indole derivatives have come to have significant clinical use.[15] Consequently, indole, indubitably can be referred to as 'privileged scaffold' in medicinal chemistry.[16] Intrigued by the significance of bicyclo[4.1.0]heptenone systems and the established literature precedents on the importance of indoles, we

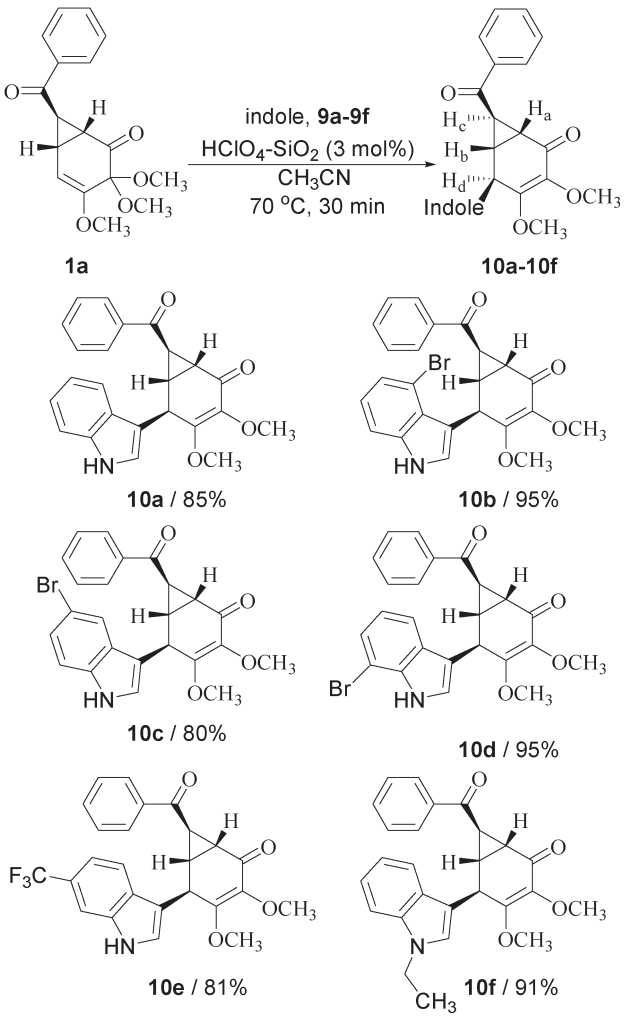


Scheme 4 Diels–Alder dimerization of MOB **5**.



Scheme 5 Synthesis of bicyclo[4.1.0]heptenone derivatives **8a**, **8a-isomer**, **8k**.

investigated the addition reactions of indole to these bicyclic systems and contemplate that their addition products may possibly be of potential use in medicinal chemistry. To begin with, reaction of compound **1a** with indole (**9a**) in the presence of catalytic amount of $HClO_4$–SiO_2[17] (3 mol%) in acetonitrile at 70 °C for 30 min provided the indolyl bicyclo[4.1.0]heptenone derivative **10a** in 85% yield (Scheme 6). Subsequently, indoles **9b–9e** were utilized in this reaction to furnish corresponding indolyl bicyclo[4.1.0]heptenone systems **10b–10e** in high yields.[18] Interestingly, *N*-ethyl indole (**9f**) also underwent a smooth addition to compound **1a** to give *N*-ethylindolyl bicyclo[4.1.0]heptenone **10f** in 91% yield indicating that free NH is not necessary for the success of the reaction.



Scheme 6 Synthesis of indolyl bicyclo[4.1.0]heptenones **10a–10f**.

Conclusions

In conclusion, we have shown that the Corey–Chaykovsky reaction applied to benzoquinone monoketals is general, convenient and a rapid procedure for the synthesis of bicyclo[4.1.0]heptenone systems with higher levels of functionality. Work toward selective cyclopropane ring opening either providing the tropolone structures or highly substituted benzene systems and studies aimed at advancing these bicyclic systems for further more transformations is being actively pursued.

Acknowledgements

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Notes and references

‡ **General procedure for the preparation of sulfonium bromide 'a'**: To phenacyl bromide (1.0 g) was added dimethyl sulfide (10 mL) and was stirred for 16 h at room temperature. Excess dimethyl sulfide was evaporated under rotory evaporation. The residual solid was triturated with methyl *t*-butyl ether and dried under vacuum to provide 1.1 g (85%) of dimethylphenacylsulfonium bromide (**a**).

General procedure for the synthesis of bicyclo[4.1.0]heptenone derivative 1a: To a stirred solution of MOB **1** (75 mg, 0.41 mmol) and S-ylide precursor '**a**' (128 mg, 0.49 mmol) in CH_3CN (3 mL) was added K_2CO_3 (140 mg, 1.02 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. After the aqueous workup and column chromatographic purification (hexanes/ethylacetate) gave **1a** (111 mg, 91%).

1a: ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 7.95–7.99 (m, 2H), 7.57–7.64 (m, 1H), 7.46–7.53 (m, 2H), 5.41 (d, J = 5.4 Hz, 1H), 3.70 (t, J = 4.2 Hz, 1H), 3.68 (s, 3H), 3.42 (s, 3H), 3.30 (s, 3H), 2.83 (ddd, J = 0.6, 4.2, 8.1 Hz, 1H), 2.62 (ddd, J = 4.2, 5.4, 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9 (C), 194.1 (C), 153.4 (C), 136.7 (C), 133.6 (CH), 128.8 (2 × CH), 128.3 (2 × CH), 99.7 (CH), 96.2 (C), 55.6 (CH3), 52.7 (CH3), 51.8 (CH3), 40.6 (CH), 33.2 (CH), 25.9 (CH) ppm. HRMS (ESI†): m/z calcd. for $C_{17}H_{18}O_5Na$ [M + Na] 325.1052; found 325.1062.

1e: ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 7.15 (d, J = 3.3 Hz, 1H), 7.05 (dd, J = 3.3, 9.3 Hz, 1H), 6.92 (d, J = 9.3 Hz, 1H), 5.40 (d, J = 5.7 Hz, 1H), 3.88 (t, J = 4.5 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 3.39 (s, 3H), 3.28 (s, 3H), 2.81 (app dd, J = 4.5, 7.8 Hz, 1H), 2.60 (ddd, J = 4.5, 5.7, 7.8 Hz,1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3 (C), 195.9 (C), 153.5 (C), 153.4 (C), 152.9 (C), 127.9 (C), 120.7 (CH), 113.9 (CH), 113.4 (CH), 100.2 (CH), 96.0 (C), 56.2 (CH3), 55.8 (CH3), 55.5 (CH3), 52.5 (CH3), 51.7 (CH3), 44.8 (CH), 33.8 (CH), 26.1 (CH). HRMS (ESI†): m/z calcd. for $C_{19}H_{23}O_7$ [M + H] 363.1444; found 363.1454.

1j: ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 7.58 (d, J = 3.9 Hz, 1H), 7.00 (d, J = 3.9 Hz, 1H), 5.38 (d, J = 5.4 Hz, 1H), 3.67 (s, 3H), 3.45 (t, J = 4.2 Hz, 1H), 3.41 (s, 3H), 3.29 (s, 3H), 2.78 (ddd, J = 0.6, 4.2, 7.8 Hz,1H), 2.63 (ddd, J = 4.2, 5.4, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5 (C), 185.6 (C), 153.5 (C), 142.3 (C), 140.8 (C), 131.9 (CH), 127.9 (CH), 99.3 (CH), 96.1 (C), 55.6 (CH3),

52.6 (CH3), 51.7 (CH3), 40.4 (CH), 32.7 (CH), 25.4 (CH). HRMS (ESI†): *m/z* calcd. for $C_{15}H_{15}ClO_5SNa$ [M + Na] 365.0226; found 365.0236.

1k: ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 5.34 (d, J = 5.7 Hz, 1H), 3.65 (s, 3H), 3.36 (s, 3H), 3.26 (s, 3H), 3.18 (t, J = 4.2 Hz, 1H), 2.53 (dd, J = 4.2, 8.1Hz, 1H) 2.38 (ddd, J = 4.2, 5.7, 8.1 Hz, 1H), 1.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.1 (C), 198.1 (C), 153.1 (C), 99.6 (CH), 96.1 (C), 55.6 (CH3), 52.7 (CH3), 51.6 (CH3), 44.1 (C), 39.6 (CH), 33.0 (CH), 25.9 (3 × CH3), 24.9 (CH). HRMS (ESI†): *m/z* calcd. for $C_{15}H_{22}O_5Na$ [M + Na] 305.1365; found 305.1377.

4j: ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 7.61 (d, J = 3.9 Hz, 1H), 7.02 (d, J = 3.9 Hz, 1H), 6.89 (dd, J = 0.6, 5.1 Hz,1H), 3.53 (t, J = 4.5 Hz,1H), 3.43 (s, 3H), 3.29 (s, 3H), 2.83 (ddd, J = 0.6, 4.5, 7.8 Hz, 1H), 2.67 (ddd, J = 4.2, 5.4, 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.0 (C), 184.8 (C), 141.8 (C), 141.5 (C), 135.2 (CH), 132.4 (CH), 128.0 (CH), 123.8 (C), 95.6 (C), 52.7 (CH3), 51.7 (CH3), 39.0 (CH), 33.2 (CH), 28.4 (CH). HRMS (ESI†): *m/z* calcd. for $C_{14}H_{12}BrClO_4SNa$ [M + Na] 412.9226; found 412.9233.

4k: ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 6.85 (dd, J = 0.6, 5.4,1H), 3.39 (s, 3H), 3.25 (s, 3H), 3.24–3.28 (m, 1H), 2.57 (ddd, J = 0.6, 4.5, 7.5 Hz, 1H), 2.45 (ddd, J = 4.5, 5.4, 7.5 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.5 (C), 195.5 (C), 135.6 (CH), 123.3 (C), 95.7 (C), 52.7 (CH3), 51.6 (CH3), 44.3 (C), 38.2 (CH), 33.5 (CH), 28.1 (CH), 25.8 (3 × CH3). HRMS (ESI†): *m/z* calcd. for $C_{14}H_{20}O_4Br$ [M + H] 331.0545; found 331.0558.

10b: ^{1}H NMR (300 MHz, DMSO-d_6): δ =11.52 (brs, 1H), 8.13–8.15 (m, 2H), 7.69–7.72 (m, 1H), 7.57–7.60 (m, 2H), 7.45 (t, J = 4.2 Hz, 1H), 7.23 (dd, J = 0.8, 7.6 Hz, 1H), 7.14 (s, 1H), 7.05 (t, J = 8.0 Hz, 1H), 5.43 (s, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.51–3.53 (m, 1H), 2.36 (ddd, J = 1.2, 3.6, 4.8 Hz, 1H), 2.27 (ddd, J = 0.8, 4.4, 5.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.9 (C), 188.9 (C), 160.2 (C), 138.1 (C), 136.4 (C), 134.8 (C), 133.7 (CH), 128.9 (2 × CH), 128.5 (2 × CH), 124.5 (CH), 123.5 (CH), 122.9 (CH), 122.9 (C) 114.7 (C), 112.1 (C), 111.9 (CH), 59.5 (CH3), 57.0 (CH3), 33.0 (CH), 32.9 (CH), 31.5 (CH), 30.8 (CH). MS (ESI†): *m/z* found $C_{24}H_{21}BrNO_4$ [M + 2 + H] 468.

10d: ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 8.36 (brs, 1H), 7.96–8.02 (m, 2H), 7.57–7.66 (m, 2H), 7.46–7.55 (m, 2H), 7.36–7.43 (m, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 4.46 (s, 1H), 3.86 (s, 3H),3.74 (s, 3H), 3.13 (dd, J = 3.6, 4.8 Hz, 1H), 2.75 (ddd, J = 1.5, 3.6, 8.1 Hz, 1H), 2.55 (ddd, J = 1.2, 4.8, 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6 (C), 190.5 (C), 159.9 (C), 137.0 (C), 135.1 (C), 134.7 (C), 133.5 (CH), 128.8 (2 × CH), 128.3 (2 × CH), 126.8 (C), 125.1 (CH), 122.8 (CH), 121.3 (CH), 117.8 (CH), 117.0 (C), 105.2 (C), 60.6 (CH3), 58.7 (CH3), 35.7 (CH), 34.9 (CH), 32.3 (CH), 28.2 (CH). MS (ESI†): *m/z* found $C_{24}H_{21}BrNO_4$ [M + 2 + H] 468.

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18 In 1D NOE studies on compound **10b**, saturation of H_d gave rise to enhancement in signal intensity of both H_b and H_c; similarly saturation of H_c gave rise to signal intensity enhancement of H_b and H_d due to conformational arrangement of the bicyclic system, making it difficult to assign the stereochemistry of the newly formed stereocentre. However, from the steric considerations, we presume the attack of indoles to compound **1a** occurred from less hindered face providing compound **10**.