# Selective Synthesis of 1,3-Substituted Cuneanes: En Route to Potent Bioisosteres of *m*-Substituted Benzenes

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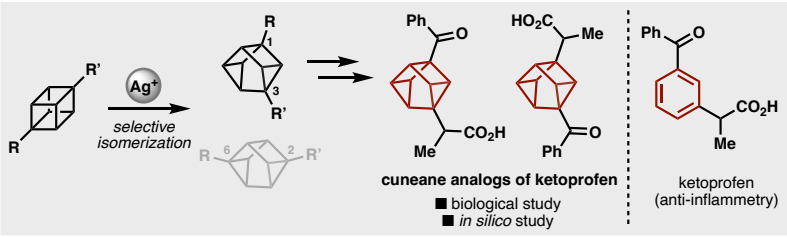
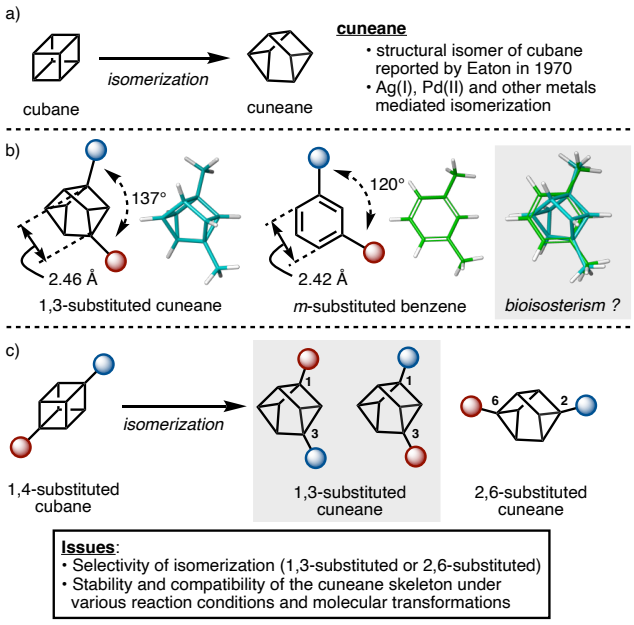



**ABSTRACT:** We herein disclose a method to obtain 1,3-substituted cuneane by selective isomerization of 1,4-substituted cubanes. The electronic property of the substituent strongly affects the iso merization ratio of 1,3-substituted cuneane and 2,6-substituted cuneane. Based on structural similarity, we considered that 1,3-substituted cuneane would be a bioisostere of *m*-substituted benzene. The synthesis of a cuneane analogs of pharmaceuticals having *m*-substituted benzene moiety and its biological and in silico evaluation are also described.

Cuneane[1], a structural isomer of cubane[2], is one of the most intriguing hydrocarbons because of its unique skeleton. In 1970, Eaton reported that treatment of cubane with Ag(I) or Pd(II) triggers structural isomerization to give cuneane (Scheme 1a).[1,3,4] Calorimetric and theoretical studies revealed that cubane obtains thermodynamic stability by its isomerization into cuneane.[5] In contrast with its behavior, the details of the interesting structural transformation and application of cuneanes into other fields of chemistry have not been fully investigated.[6] One of the plausible reasons why the study of cuneane is untouched would be that chemists did not try to discover the usefulness of the exotic hydrocarbons.

Recently, pharmaceutical applications of caged hydrocarbons have been investigated and it has been revealed that some of these hydrocarbons f,,unction as bioisosteres of benzene rings with distinct types of substitution patterns.[7] However, most of these examples are applied to bioisostere of mono- or *para*-substituted benzene. Bioisosteres of *ortho*- or *meta*-substituted benzene are under investigation. However, investigations of their bioactivities have rarely been conducted.[8]

In our recent attempt to expand the utility of caged hydrocarbons as bioisosteres[9] and on the basis of the structural similarity of aromatics and caged hydrocarbons, we reached the following hypothesis: 1,3-substituted cuneanes may work as bioisosteres of *m*-substituted benzenes (Scheme 1b); computational structural investigation revealed that 1,3-substituted cuneanes have a similar distance and angle between two substituents with *m*-substituted benzene.[10]

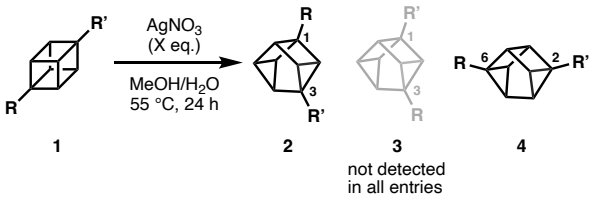



**Scheme 1: Cuneane: synthesis, structure, and its potential application for bioisosteres of *m*-substituted benzene**

1,3-substituted cuneanes are synthesized by the isomerization of 1,4-substituted cubanes.

However, there are three plausible isomerized products of 1,4-substituted cubane having different substituents, that is, two different 1,3-substituted cuneanes and a 2,6-substituted cuneane (Scheme 1c). To demonstrate our hypothesis, a

**Table 1: Isomerization of 1,4-substituted cubanes into 1,3- and 2,6-substituted cuneanes**

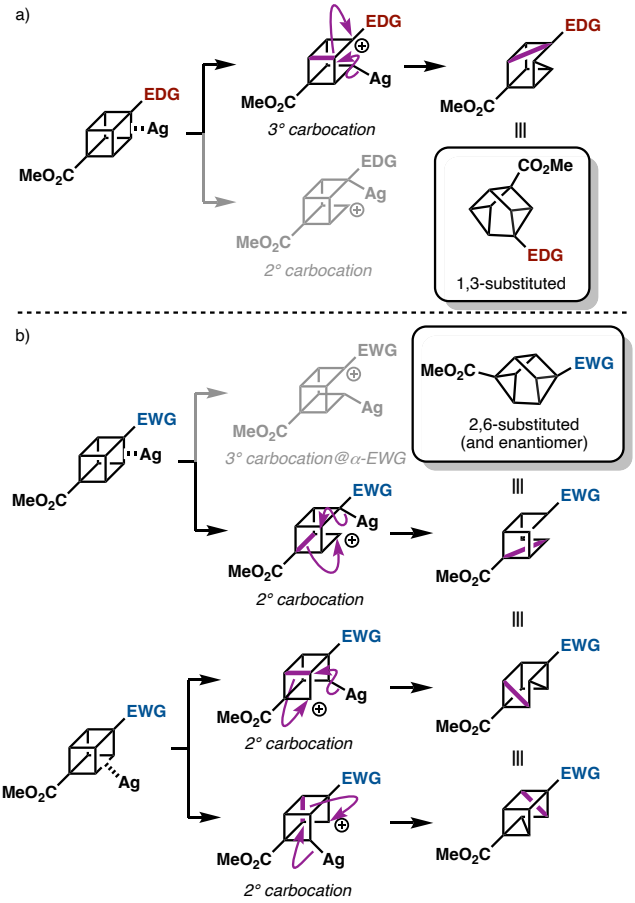



| Entry | R | R' | X | Yield | 2:4 |
|---|---|---|---|---|---|
| 1 (**1a**) | $CO_2Me$ | $CO_2Me$ | 2 | 73% | 1:>20 |
| 2 (**1b**) | $CH_2OH$ | $CH_2OH$ | 4 | 81% | 12:1 |
| 3 (**1c**) | $CH_2OAc$ | $CH_2OAc$ | 4 | 88% | 5:1 |
| 4 (**1d**) | $CO_2Me$ | $CH_2OH$ | 0.05 | 88% | 8:1 |
| 5 (**1e**) | $CO_2Me$ | $CH_2OAc$ | 1 | 66% [a] | 2:1 |
| 6 (**1f**) | $CO_2Me$ | $CH_2OMOM$ | 0.05 | 64% | 5:1 |
| 7 (**1g**) | $CO_2Me$ | Ph | 0.05 | 97% | >20:1 |
| 8 (**1h**) | $CO_2Me$ | $CON^iPr_2$ | 4 | 65% [b] | 1:>20 |
| 9 (**1i**) | $CO_2Me$ | CN | 4 | 68% [b] | 1:>20 |
| 10 (**1j**) | $CO_2Me$ | $CHCHCO_2Et$ | 0.05 | 93% | 1:1.7 |
| 11 (**1a**)[c] | $CO_2Me$ | $CO_2Me$ | 1 | 99% | 1:5 |
| 12 (**1d**)[c] | $CO_2Me$ | $CH_2OH$ | 0.05 | 96%[d] | >20:1 |
| 13 (**1e**)[c] | $CO_2Me$ | $CH_2OAc$ | 0.05 | 93%[e] | 15:1 |
| 14 (**1j**)[c] | $CO_2Me$ | $CHCHCO_2Et$ | 0.05 | 93%[f] | 1:1.5 |

[a]12 h, [b]48 h [c]1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) instead of MeOH/$H_2O$ was used as a solvent. [d]3 h [e]9 h [f]8 h

synthetic methodology to selectively obtain 1,3-substituted cuneane should be used. Furthermore, there are limited insights about the stability and compatibility of the cuneane skeleton under various reaction conditions and molecular transformations. Herein, we describe a selective synthesis of 1,3-disubstituted cuneanes from 1,4-substituted cubanes.[11] We also describe the synthesis and biological evaluation of cuneane analog of pharmaceuticals with *m*-substituted benzene.[12]

Our study started with the investigation of substituent effect for the isomerization of cubane into cuneane. We tried isomerization of various 1,4-substituted cubanes into cuneanes (Table 1, entry 1–10). We employed the reaction conditions using silver nitrate as reagent or catalyst in MeOH/$H_2O$ solvent.[13] Symmetrically substituted 1,4-substituted cubanes (R=R', entries 1–3) were isomerized efficiently and gave corresponding cuneanes with varying regioisomer ratios. Isomerization of cubane **1a** and **1b** has already been conducted by Eaton[1] under slightly different conditions, and they reported almost the same ratio of 1,3-substituted cuneanes **2** and 2,6-substituted cuneanes **4**. Next, differentially substituted 1,4-substituted cubanes (R≠R'; R=$CO_2Me$; entries 4–10) were examined, and a significant substituent effect was observed. When electron donating group (EDG) such as alkyl or aryl substituent was substituted as R' group, 1,3-substituted cuneanes were obtained preferentially (entry 4–7). In contrast, when electron withdrawing group (EWG) such as amide, nitrile, and unsaturated ester substituent was substituted as R' group, 2,6-substituted cuneanes were obtained preferentially (entry 8–10).




**Scheme 2: Mechanistic explanation of selective isomerization**

Note that the regioisomer of 1,3-substituted cuneanes (**3**) was not observed in all entries.

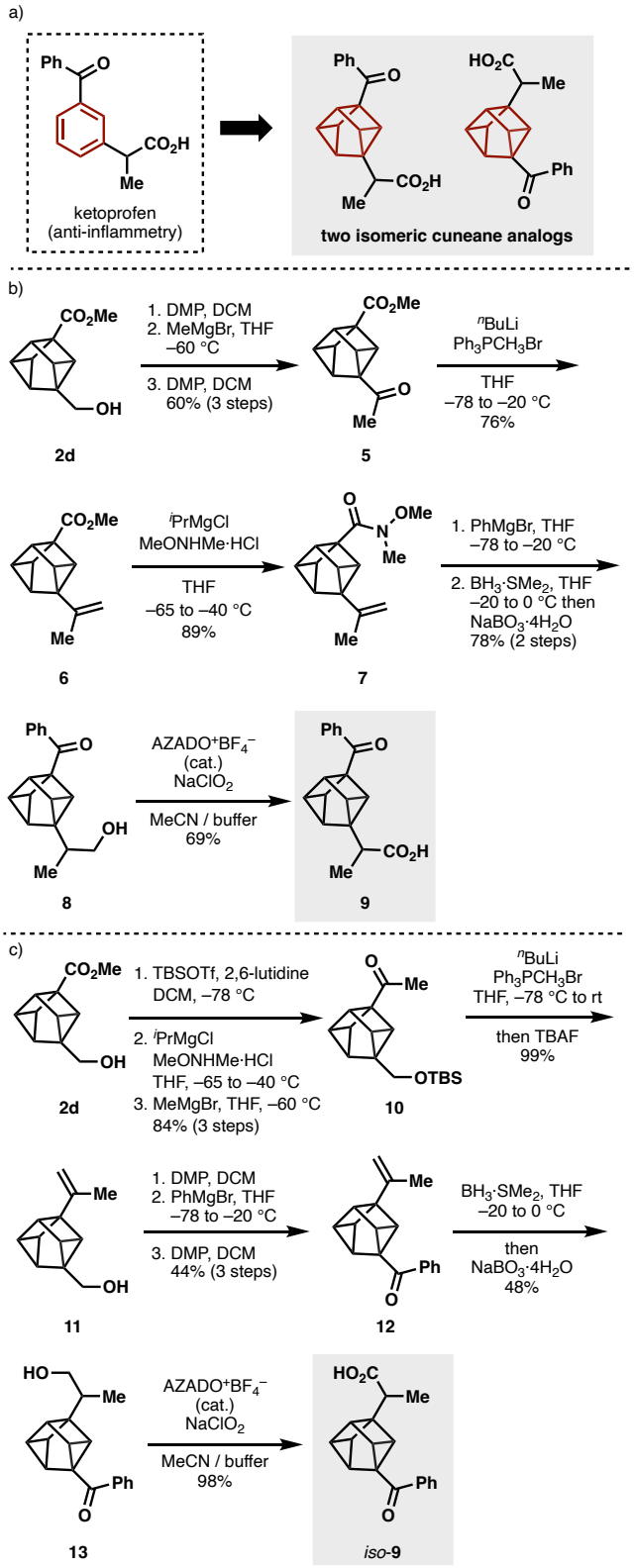
On the basis of the reported reaction mechanism of Ag(I)-mediated isomerization of cubane, we considered the reason for the occurrence of selective isomerization and the rational explanation of the substitution effect on cubane (Scheme 2). Halpern and coworkers reported that this isomerization proceeded via cationic rearrangement.[14] According to this mechanism isomerization should proceed to pass through favorable carbocation species. Therefore, 1,4-substituted cubanes with EDG underwent isomerization to generate stable tertiary carbocation (Scheme 2a). Note that the substrate with free hydroxyl group improves the ratio of 1,3-substituted cuneane because of the directing effect of Ag(I) as suggested by Eaton. Protection of the hydroxyl group diminished this directing effect, and electronic induction by the oxygen atom and the pendant protecting group caused a decrease in the ratio of 1,3-substituted cuneane. In contrast, 1,4-substituted cubanes with an EWG avoided forming the same tertiary carbocation because it was destabilized by an a-carbonyl group (Scheme 2b). Relatively stable secondary carbocation would be generated in this case, and following rearrangement, predominantly 2,6-substituted cuneanes would be generated. 2,6-substituted cuneane would also be generated by Ag-mediated activation of an "unbiased" C–C bond.

Based on this mechanistic consideration, we hypothesized that solvent-induced stabilization of carbocation may accelerate the reaction rate and change the ratio of 1,3- and 2,6-substituted cuneane. The isomerization of some 1,4-substituted cubanes in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[15] was assessed (Table 1 entry 11–14). Generation of 1,3-$CO_2$Me cuneane **2a**, which was not detected in the MeOH/$H_2O$ solvent (**1a**), and generation of 1,3-substituted cuneane was significantly improved in alkyl-substituted cubane (**1d**, **1e**).

With the preparative route to obtain differentially substituted 1,3-substituted cuneane, we conducted cuneane analog synthesis of pharmaceuticals with *m*-substituted benzene. We chose ketoprofen, a non-steroidal anti-inflammatory drug with a nonselective cyclooxygenase (COX) inhibitory activity, as a target compound. Note that there are two plausible isomeric analogs because of the asymmetric nature of 1,3-substituted cuneane (Scheme 3a). We synthesized both isomers and evaluate these COX-2 inhibitory activity. After several failed attempts, we started the synthesis with cuneane alcohol **2d** which is obtained in good yield from the corresponding 1,4-substituted cubane **1d** (Scheme 3b). Primary alcohol **2d** was successively converted into methyl ketone **5** using a three-step oxidation-Grignard reaction-oxidation sequence. The resulting carbonyl group was converted into exo-methylene by the conventional Wittig reaction to give ester **6**. Next, the methoxycarbonyl group of **6** was converted into Weinreb amide **7**. The addition of phenylmagnesium bromide following hydroboration–oxidation gave primary alcohol **8** in good yield. Finally, the one-pot oxidation protocol of primary alcohol that we developed[16] successively gave the desired cuneane analog of ketoprofen **9** in good yield. Note that analog **9** was obtained as a mixture of four stereoisomers because **9** has one asymmetric scaffold (1,3-substituted cuneane)[4b,17] and one asymmetric carbon. Similarly, *iso*-**9** was synthesized from alcohol **2d** (Scheme 3c) . These synthetic explorations also demonstrate the compatibility and stability of the cuneane skeleton under the conditions of the conventional molecular transformation.

We evaluated the cyclooxygenase-2 (COX-2) inhibitory activity of ketoprofen and cuneane analogs **9** and *iso*-**9** (a mixture of four stereoisomers, respectively) by measuring prostaglandin $E_2$ ($PGE_2$) production using a lipopolysaccharide-stimulated human leukemic monocyte cell line (Figure 1). The cuneane analog **9** showed 100 times less activity than the original ketoprofen. Interestingly, *iso*-**9** exhibited no COX-2 inhibitory activity. These results indicate that potential applicability of cuenanes into bioisostere of *m*-substituted benzenes and, importantly, position of substituent plays a crucial role for bioactivity.

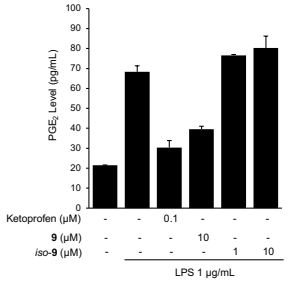
To understand the relationship between molecular structure and bioactivity, we conducted the in silico studies including docking and molecular dynamics (MD) simulation for protein-ligand interaction analysis.[10] From initial docking study of ketoprofen, analog **9**, and *iso*-**9** with COX-2 showed that these three compounds appeared to fit well in the ligand pocket of COX-2. In addition, MD simulation to optimize docking poses and assess stability revealed that some relative changes of cuneane analogs **9** and *iso*-**9** from the initial docking pose than ketoprofen in the binding pocket (Figure 2). Cuneane analog **9** moved about 3Å from the initial docking pose but then remained stable in the same binding site. *Iso*-**9** has not changed




**Scheme 3: Synthesis of the cuneane analog of ketoprofen 9 and *iso*-9**

significantly in position from its initial binding site but remains unstable with large fluctuations. MD simulation also revealed that *iso*-**9** could only retain an ionic interaction with

Arg120 residue compared with both ketoprofen and **9** interacting with at least 3 residues, Arg120, Tyr355, and Ser530[10] and this significantly indicated the plausible reason why *iso*-**9** showed no biological activity. Docking score of these three ligands after minimization via MD simulation (prepared structure of 100 nsec after the initial structure) also suggest the significant unfitness of *iso*-**9** for COX-2 binding and a difference in activity between ketoprofen and **9** (Figure 3).




| | Concentration (μM) | Inhibition rate of PGE2 production (%, mean ± SEM) |
|---|---|---|
| Ketoprofen | 0.1 | 64 ± 5 ** |
| **9** | 0.1 | -3 ± 16 |
| | 1 | 29 ± 15 |
| | 10 | 50 ± 10* |

*$p$<0.05, **$p$<0.01 vs. LPS alone

**Figure 1: Comparison of COX-2 inhibitory activity of ketoprofen and its cuneane analog 9 and *iso*-9**

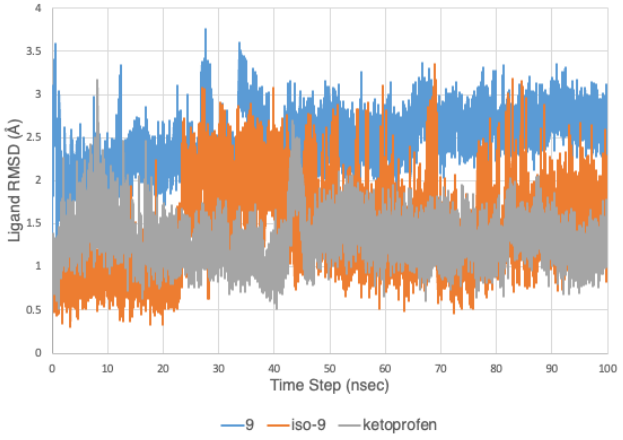
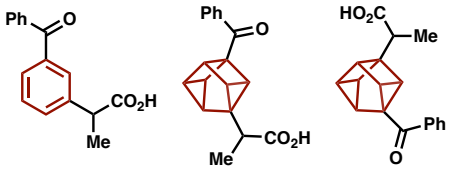



**Figure 2: Ligand RMSD (root mean square deviation) values during MD simulations**



| | ketoprofen | **9** | *iso*-**9** |
|---|---|---|---|
| docking score (kcal/mol) | –9.402 | –9.035 | –6.840 |
| ligand efficiency | 0.495 | 0.430 | 0.326 |

**Figure 3: Docking score of three ligands with COX-2 after 100 nsec MD simulations**

We have disclosed a selective synthesis of 1,3-substituted cuneanes, which is a potential bioisostere of m-substituted benzenes, from 1,4-substituted cubanes and revealed that the substituent strongly affects the ratio of 1,3- and 2,6-substituted cuneanes. Furthermore, we succeeded in synthesizing the two plausible cuneane analogs of ketoprofen with applicable reactions. Our group is currently conducting ongoing studies to apply a cuneane skeleton to pharmaceutical usage, including enantioselective isomerization of 1,4-substituted cubane into 1,3-substituted cuneane.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental detail and spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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(10) See Supporting Information for details.

(11) During preparation of the manuscript, two different research groups independently reported the silver(I)-catalyzed or mediated selective isomerization of 1,4-substituted cubanes into 1,3- or 2,6-substituted cuneanes and its application to isosteres. See; a) Son, J.-Y.; Aikonen, S.; Morgan, N.; Harmata, A. S.; Sabatini, J. J.; Sausa, R. C.; Byrd, E. F. C.; Ess, D. H.; Paton, R. S.; Stephenson, C. R. J. Exploring Cuneanes as Benzene Isosteres and Energetic Materials: Scope and Mechanistic Investigations into Regioselective Rearrange-Ments from Cubanes. *J. Am. Chem. Soc.* **2023**, doi: 10.1021/jacs.3c03226 (*ChemRxiv.* **2023**, doi: 10.26434/chemrxiv-2023-0xn9c) b) Smith, E.; O' Brien, L.; Jones, K. D.; Argent, S. P.; Salome, C.; Lefebvre, Q.; Valery, A.; Newton, G. N.; Lam, H. W. Silver(I)-catalyzed synthesis of cuneanes from cubanes and their investigation as isosteres. *J. Am. Chem. Soc.* **2023**, doi: 10.1021/jacs.3c03207 (*ChemRxiv.* **2023**, doi: 10.26434/chemrxiv-2023-l8q0t)

(12) We have deposited this manuscript to ChemRxiv as follows. Fujiwara, K.; Nagasawa, S.; Maeyama, R.; Segawa, R.; Hirasawa, N.; Hirokawa, T.; Iwabuchi, Y. Selective Synthesis of 1,3-Disubstituted Cuneanes: En Route to Potent Bioisosteres of *m*-Substituted Benzenes. *ChemRxiv* **2023**, doi:10.26434/chemrxiv-2023-fgxxm.

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