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ALUMINIUM-MEDIATED [4 + 1] CYCLIZATION REACTION: NOVEL SYNTHESIS OF 2,2,5,5-TETRAMETHYLCYCLOPENTANECARBOXYLIC ACID

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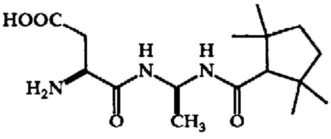
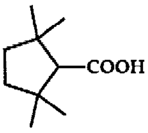
A new [4 + 1] cyclization reaction mediated by aluminium is developed and applied to the synthesis of 2,2,5,5-tetramethylcyclopentanecarboxylic acid, a part of an artificial sweetner.

An artificial sweetner *N*-(*L*-aspartyl)-1,1-diaminoalkane (**1**), called *Gem Sweet*, has been found to be 800-1000 times as sweet as sucrose.[1] It is non-caloric, free of bitter aftertaste, and thermally more stable than *Aspartame*. The structural analysis of **1** shows that it is a gem diamino compound linked to L-aspartic acid on one side and to 2,2,5,5-tetramethylcyclopentanecaboxylic acid (**2**) on the other side with an amide linkage. Its unique sweetness and structural simplicity generated curiosity, which led us to discover a novel [4 + 1] cyclization reaction to build up **2**, the only possible synthetic target in this molecule. The new synthetic reaction is the subject of this communication. Our synthetic strategy is a Lewis acid-mediated reaction of tertiary 1,4-dihalide **3** with a C_2 metal reagent like metal acetylide to give functionalized tetramethylcyclopentane **4**, which then can be converted into **2**.



Gem Sweet **1**



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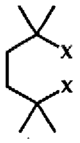

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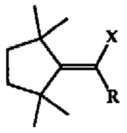

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After many unfruitful reactions, our aim was realized when alkynylalanes R_nAlCl_{3-n} (**5**)[2] were reacted with 1,4-dihalides[3] **3** (Scheme 1). The results are summarized in Table 1. The expected [4 + 1] cyclization product **4** was isolated in moderate to good yields. The reaction between **3a** (2 mol) and tri(phenylethynyl)alane (**5a**$_3$, 0.33 mol or 1 mol of PhC≡C moiety) afforded **4a** in 44% yield (phenylacetylene base, entry 2); the reaction of **3b** and **5a**$_3$ produced **4b** in 58% yield (entry 3). The reaction between **3a** and **5b**$_3$ afforded **4c** in 45% yield (entry 7). In contrast, equimolar reaction of **5a**$_3$ with **3a** gave **6** only. In addition, Cl-containing aluminium reagent gave fair amount of a tricyclic product **6**.

It is likely that the mechanism of this reaction (Scheme 2) involves initial alkynylation at tertiary center[4] to form an intermediate **7** and subsequent activation of its C-X bond by the coproduced haloaluminium reagent, followed by an intramolecular nucleophilic attack of a triple bond to give a vinyl cation **8**. This is quenched by a halide ion which already has been present in the reaction system to afford the desired product **4**. The 1 : 2 product **4d** (entry 8) should have been resulted from alkynylation of the vinyl cation **8** in the presence of an excess of the reagent **5**. The reaction of **3a** and **3b** with tri(hexynyl)alane (**5c3**) afforded a 1 : 2 product **3e** (entry 9), though the reagent was not used in excess. Replacement of Al with Zn, B or Ti resulted in either no reaction or formation of a multiproduct mixture.

Scheme 1

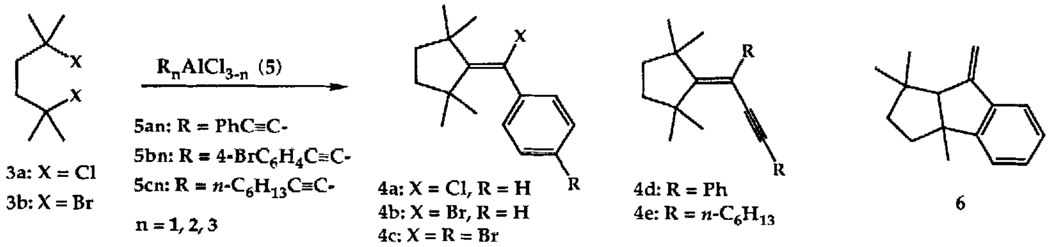


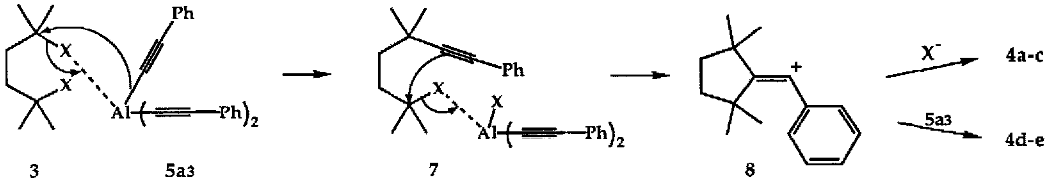
Table 1 Aluminium-mediated [4 + 1] Cyclization

Entry	3 (mol equiv)	5an (mol equiv)	Temperature[a]	Product (% yield)[b]	
1	**3a**, 2.0	**5a1**, 1.00	0 °C	**4a** (30)	**6** (35)
2	**3a**, 2.0	**5a3**, 0.33	0 °C	**4a** (44)	**6** (trace)
3	**3b**, 2.0	**5a3**, 0.33	0 °C-r.t.	**4b** (58)	**6** (trace)
4	**3b**, 1.2	**5a3**, 0.33	-20 °C-r.t.	**4b** (46)	**6** (trace)
5	**3b**, 2.0	**5a2**, 0.66	-78 °C-r.t.	**4b** (29)	**6** (7)
6	**3b**, 2.0	**5a1**, 1.00	-78 °C-r.t.	**4b** (trace)	**6** (22)
7	**3b**, 2.0	**5b3**, 0.33	0 °C-r.t.	**4c** (45)[c]	
8	**3a**, 0.5	**5a3**, 0.33	0 °C	**4d** (80)[d]	
9	**3b**, 2.0	**5c3**, 0.33	0 °C-r.t.	**4e** (22)	

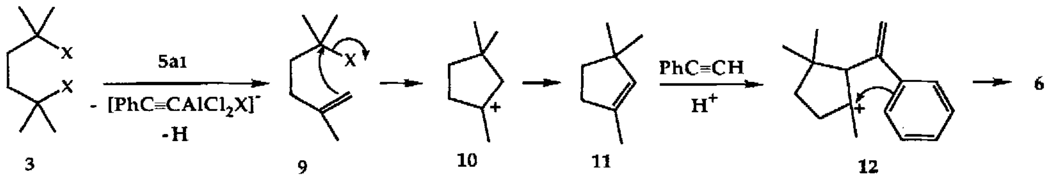
a: All the reaction was carried out in hexane-dichloromethane for a period of a couple of hours.
b: Based on the acetylene used. *c*: Many byproducts were accompanied. *d*: Based on the dichloride **3a**.

The formation of **6** is quite intriguing. It is likely, though not certain, that the high Lewis acidity of the aluminium reagent **5a1** or **5a2** may be triggering unusual sequence of reactions (Scheme 3) by dehydrohalogenating the compound **3** leading to an olefin **9**, which in turn cyclizes in the presence of the Lewis acid reagent. The intermediate **10** may lose a proton giving rise to an olefin **11**. This reacts with phenylacetylene (formed by the reaction of byproduct HX with the aluminium reagent) to give an intermediate **12**, which then undergoes the intramolecular Friedel-Crafts alkylation to complete the sequence.

Scheme 2



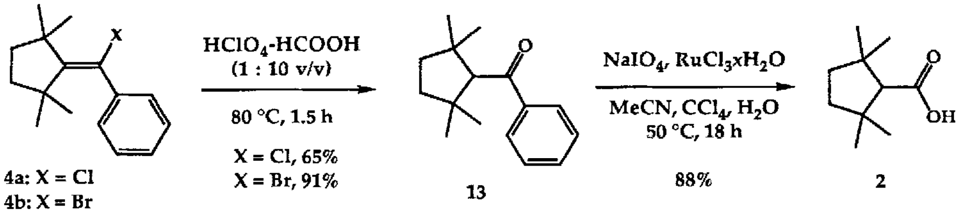
Scheme 3



A typical experimental procedure for the preparation of **4b** (run 3 in Table 1) follows. Lithium phenylacetylide was prepared by adding butyllithium (0.65 ml of 1.55 M solution, 1.0 mmol) at 0 °C to phenylacetylene (110 ml, 1.0 mmol) dissolved in hexane (4 ml) and by stirring the resulting mixture for 30 min. Aluminium chloride (44 mg, 0.33 mmol) was added, and the mixture was stirred for 1 h at 0 °C. The hexane was removed under vacuum, and dichloromethane (5 ml) as well as dibromide **3b** (0.54 g, 2.0 mmol) was added at once at -15 °C. The reaction mixture was stirred at -15 °C for 3 h and at room temperature for 1 h and passed through a short silica gel column. Concentration followed by purification by preparative TLC (silica gel, hexane) gave **4b** (0.17 g, 58% yield).[5]

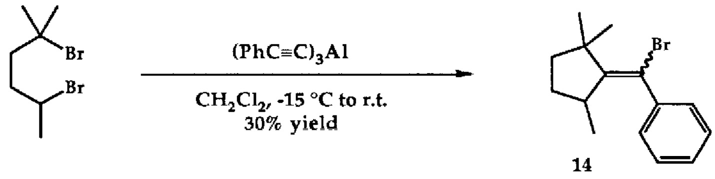
To complete the synthesis of our target, cyclic vinyl halides **4a** and **4b** were converted into **2** in a two-step sequence (Scheme 4). Thus **4a** and **4b** were hydrolyzed with $HClO_4$-HCOOH to afford phenyl ketone **13** (X=Cl, 65%; X=Br, 91%), which was further oxidized with $NaIO_4$ in the presence of catalytic amount of $RuCl_3.xH_2O$ to give **2** (mp 127 °C, lit.,[1d] 127-129 °C) in 88% yield.

Scheme 4



We also investigated the scope and limitations of the [4 + 1] cyclization reaction. F example, we were successful in applying this methd to 2,5-dibromo-2-methylhexane (Scheme which on reaction with tri(phenylethynyl)alane afforded the required cyclic product **14** in 30 yield.

Scheme 5



The cyclopentane synthesis reported herein is based especially on a novel cation-induc ring closure (e.g. **7** → **8**) and allows us to form a tertiary-vinyl C-C bond. With this repect, t present methodology contrasts sharply to the five-membered ring formation via intramolecul carbometallation[6a] or radical cyclization.[6b] Work is in progress on its synthetic application.

References and Notes

1 (a) Verlander, M. S.; Fuller, W. D.; Goodman, M. *European Patent,* 0128654 (A2), **1984**; *Che Abstr.* **1985,** *102,* 185492c. (b) Fuller, W. D.; Goodman, M.; Verlander, M. S. *J. Am. Chem. S* **1985,** *107,* 5821. (c) Goodman, M.; Coddington, J.; Mierke, D. F. *J. Am. Chem. Soc.* **1987,** *1C* 4712. (d) Mayr, H.; Heilmann, W.; Vorbruggen, H. *Deutsches Patentamt,* 3534613(A1), **198** *Chem. Abstr.* **1987,** *107,* 115282p. (e) Nummy, L. J.; Corkins, H. G.; Scarano, L. S.; Byrne, D. *PCT International* WO 87/03278, **1987**; *Chem Abstr.* **1989,** *110,* 57174d. (f) Yamanouchi, Hattori, K.; Ikeda, S.; Tamaki, K. *Japan Kokai Tokkyo Koho,* 61-200940; *Chem. Abstr.* **198** *106,* 32412j.

2 The organoalanes of a general formula **5** were prepared *in situ* via the corresponding alky 1-yllithium derivatives, prepared from the corresponding alkynes using one equivalent of BuLi in hexane, by treating with appropriate equivalents of $AlCl_3$. Use of $AlBr_3$ was of advantage. Reagent of type $Et_2AlC{\equiv}CPh$ gave the tricyclic compound **6** as the major produc

3 Prepared by the reaction of commercially available 2,5-dimethyl-2,5-hexanediol wi hydrochloric or hydrobromic acid in the presence of sulfuric acid catalyst.

4 Negishi, E.; Baba, S. *J. Am. Chem. Soc.* **1975,** *97,* 7385.

5 When the experiment was repeated using **5a**$_3$ (1.33 mmol) and **3b** (8 mmol), **4b** (0.64 g, bp 1 150 °C/1 Torr) and recovered **3b** (1.15 g, bp 70-90 °C/1 Torr) were isolated. Thus yield of was 54% based on phenylacetylene or 64% based on the consumed starting dibromide.

6 (a) Cyclization of 5-alkyn-1-yllithium: Bailey, W. F.; Ovaska, T. V.; Leipert. T. K. *Tetrahedr Lett.* **1989,** *30,* 3901 and references cited therein. See also Fujikura, S.; Inoue, M.; Utimoto, Nozaki, H. *Tetrahedron Lett.* **1984,** *25,* 1999. (b) Atom transfer radical cyclization of hex ynyl iodides: Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1989,** *111,* 6265 and t references cited therein.

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