

0040-4039(95)01100-5

Total Synthesis of (-)-trans-Kumausyne

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Abstract: The total synthesis of (-)-trans-kumausyne has been accomplished in an enantiospecific fashion starting from an L-arabinose derivative. The key step is the stereoselective formation of the substituted tetrahydrofuran via novel cyclization of the β -silyl cation intermediate, generated by the addition of allylsilane to di-O-isopropylidene-aldehydo-arabinose in the presence of boron trifluoride etherate.

(-)-trans-Kumausyne is a brominated C₁₅-nonterpenoid compound, which consists of a tetrahydrofuran framework with unique enyne and bromohexenyl side chains, isolated in 1983 from the red alga Laurencia nipponica Yamada.¹ The elegant synthesis of (\pm) -trans-kumausyne has been reported by Overman et al. in 1991 via the stereocontrolled formation of a hydrobenzofuranone derivative starting from 1-vinylcyclopentenediol and α -(benzyloxy)acetaldehyde.² Although several approaches to the tetrahydrofuran skeleton of kumausyne, including enantioselective methods, have been presented by other groups,³⁻⁵ no total synthesis of the optically pure form has been accomplished to date.



(-)-trans-kumausyne (1)

Herein, we describe the first enantioselective synthesis of (-)-*trans*-kumausyne using a previously reported method for the stereoselective formation of substituted tetrahydrofurans; the BF₃-promoted reaction of 2,3-O-isopropylidene derivatives of *aldehydo*-aldose with allylsilanes *via* cyclization of the β -silyl cation intermediates (Scheme 1).⁶



SCHEME 1

Our synthesis of 1 started from 2,3;4,5-di-O-isopropylidene-aldehydo-L-arabinose (2), obtained from Larabinose in a three-step sequence,⁷ and allyldimethylphenylsilane whose Si-C bond can be converted into a hydroxyl group by the Tamao⁸-Fleming⁹ oxidation at a later time. The reaction of 2 with the allylsilane was promoted by boron trifluoride etherate in a highly stereoselective manner to give cycloadduct 3 in 73% yield as the sole diastereomer. A normal allylation product, homoallyl alcohol 4, was also isolated in 12% yield from this reaction. The obtained 3 contains the same configuration at all stereogenic centers on the tetrahydrofuran ring as (-)-trans-kumausyne.



Lactone 11, a precursor for the introduction of the enyne and bromohexenyl side chains, was straightforwardly derived from cycloadduct 3 as outlined in Scheme 2. The isopropylidene groups of 3 were removed in high yield using an ion-exchange resin (H⁺-form). One carbon degradation of the resulting tetraol 5 was carefully carried out by treatment with 1.1 equivalent of NaIO₄ to afford lactol 6 in 72% yield. In order to protect the hemiacetal portion against the following deoxygenating and acidic conditions, lactol 6 was temporarily converted into the corresponding lactone 7 by selective oxidation with *N*-iodosuccinimide (NIS)-tetrabutylammonium iodide.¹⁰ The hydroxyl group of 7 was then deoxygenated by the Barton–Robins procedure,¹¹ providing 8 in 77% overall yield. Subsequently, oxidative cleavage of the Si–C bond of lactone 8 was best accomplished by using Fleming's reagent (AcOOH–Hg(OAc)₂ in AcOH),⁹ which gave the desired alcohol 9 in 71% yield accompanied by 16% of its acetate derivative 10. This acetate was easily converted into 9 by basic hydrolysis. Protection of the hydroxyl group in 9 with *t*-BuPh₂SiCl led to lactone 11.



SCHEME 2

a) Dowex $50W^{\textcircled{0}}$ (H⁺), EtOH-H₂O, 60 °C, 3 h, 91%. b) NalO₄ (1.1 equiv.), EtOH-H₂O, 0 °C to r.t., overnight, 72%. c) NIS (2.5 equiv.), Bu₄NI (1 equiv.), CH₂Cl₂, r.t., 3.5 h, 82%. d) PhOC(S)Cl (1.2 equiv.), DMAP (2.1 equiv.), MeCN, r.t., 20 h, 80%. e) Bu₃SnH (1.5 equiv.), AIBN (0.2 equiv.), toluene, reflux, 1 h, 96%. f) AcOOH, Hg(OAc)₂ (1.5 equiv.), AcOH, 67 °C, 5.5 h, **9**; 71%, **10**; 16%. g) Ba(OH)₂, 0 °C, 1.5 h, 73%. h) *t*-BuPh₂SiCl (1.7 equiv.), imidazol (2 equiv.), CH₂Cl₂, 19 h, 85%.

The enyne and 1-bromo-3-hexenyl side chains were constructed as outlined in Scheme 3. After lactone 11 was reduced to lactol 12 by exposure to diisobutylaluminum hydride, the enyne side chain was introduced by the Wittig reaction using two equivalents of (3-trimethylsilyl-2-propynyl)triphenylphosphorane.¹² The expected (*E*)-isomer 13 was obtained in 81% yield as a major product (E:Z=12:1) which is separable by silica gel chromatography. Acetylation of 13 followed by removal of the both trimethylsilyl and *t*-butyldiphenyl-silyl groups gave the primary alcohol, which was then converted into aldehyde 15 by the Swern oxidation. The elaboration of the (*E*)-1-bromo-3-hexenyl side chain was accomplished by Overman's protocol, which has been developed during their total synthesis of (±)-kumausyne.² Treatment of aldehyde 15 with 3-trimethylsilyl-1-pentene in the presence of boron trifluoride etherate led to the desired linear adduct as a single isomer.¹³ Subsequent bromination using triphenylphosphine–carbon tetrabromide in the presence of 2,6-di-*t*-butylpyridine led to (–)-*trans*-kumausyne 16. Each of the synthetic samples gave ¹H and ¹³C NMR spectra consistent with those from the natural material; the specific rotations for 1 and 16 were [α]_D²⁸ +6.9° (*c*, 0.41, CHCl₃) [lit.¹ [α]_D²⁰ +6.5° (*c*, 1.08, CHCl₃)], respectively.



i) i-Bu₂AlH, THF, -78 °C, 5 h, quant. j) TMSC=CCH₂PPh₃·Br+BuLi (2.2 equiv.), THF, -78 °C to r.t., 5 h, 88% (E:Z=12:1). k) Ac₂O, pyridine, r.t., overnight, 99%. l) Bu₄NF (2.2 equiv.), THF, r.t., 3 h, 87%. m) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to r.t., 4 h, 97%. n) CH₂=CHCH(SiMe₃)CH₂CH₃, BF₃·OEt₂, CH₂Cl₂, -78 °C to r.t., 4.5 h, 58%. o) Ph₃P, CBr₄, 2,6-di-*t*-butylpyridine, benzene, 40 °C, 40 min, 26%. p) K₂CO₃, MeOH, r.t., 1.5 h, 87%.

Further investigations are in progress on the application of these processes to other brominated tetrahydrofuran-nonterpenoids isolated from the red alga genus *Laurencia*.

Acknowledgment. We thank Prof. Teruaki Mukaiyama (Science University of Tokyo) for his helpful discussions and Prof. Minoru Suzuki (Hokkaido University) for providing the comparison spectra of (-)trans-kumausyne and a reprint of reference 1.

REFERENCES AND NOTES

- 1. Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. Chem. Lett. 1983, 1643-1644.
- 2. Brown, M. J.; Harrison, T.; Overman, L. E. J. Am. Chem. Soc. 1991, 113, 5378-5384.
- 3. Tonn, C. E.; Palazón, J. M.; Ruiz-Pérez, C.; Rodríguez, M. L.; Martín, V. S. Tetrahedron Lett. 1988, 29, 3149-3152.
- 4. Stuart, J. G.; Nicholas, K. M. Heterocycles 1991, 32, 949-963.
- 5. Andrey, O.; Landais, Y. Tetrahedron Lett. 1993, 34, 8435-8438.
- 6. Sugimura, H. J. Syn. Org. Chem., Jpn. 1993, 51, 884–893 (Japanese): Sugimura, H. Tetrahedron Lett. 1990, 31, 5909–5912.
- 7. Zinner, H.; Wittenburg, E.; Rembarz, G. Chem. Ber. 1959, 92, 1614-1617.
- Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. Organometallics 1983, 2, 1694-1696: Tamao, K.; Ishida, N.; J. Organomet. Chem. 1984, 269, C37-C39.
- Fleming, I.; Henning, R.; Plaut, H. J. Chem. Soc., Chem. Commun. 1984, 29-31: Fleming, I.; Sanderson, P. E. J. Tetrahedron Lett. 1987, 28, 4229-4232: Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. J. Chem. Soc., Perkin Trans. 1 1995, 317-337.
- 10. Hanessian, S.; Wong, D. H.; Therien, M. Synthesis, 1981, 394-396.
- 11. Robins, M. J.; Wilson, J. S.; Hansske, F. J. Am. Chem. Soc. 1983, 105, 4059-4065.
- 12. Corey, E. J.; Ruden, R. A. Tetrahedron Lett. 1973, 1495-1499.
- 13. Other methods for the allylation to aldehyde 15 were briefly examined without success. When the Hiyama-Nozaki conditions¹⁴ were applied to 15, internal addition exclusively proceeded to quantitatively produce the branched adduct 17 as a diastereomeric mixture (5:1) (Eq. 1). The cobalt(II)-promoted addition of the allylic tin compound¹⁵ resulted in the production of an undesirable stereoisomer probably due to rapid epimerization of aldehyde 15 under the reaction conditions (Eq. 2).



- Okude, Y.; Hirano, S.; Hiyama, T.; Nazaki, H. J. Am. Chem. Soc. 1977, 99, 3179: Hiyama, T.; Kimura, K.; Nozaki, H. Tetrahedron Lett. 1981, 22, 1037-1040: Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. Bull. Chem. Soc. Jpn. 1982, 55, 561-568.
- 15. Iqbal, J.; Joseph, S. P. Tetrahedron Lett. 1989, 30, 2421-2422.

(Received in Japan 26 April 1995; revised 8 June 1995; accepted 14 June 1995)