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COMPLETE ASYMMETRIC INDUCTION IN HETEROCONJUGATE ADDITION ON AN ACYCLIC SYSTEM

A NEW SYNTHETIC APPROACH DIRECTED TOWARD ANSAMACROLIDE MAYTANSINE

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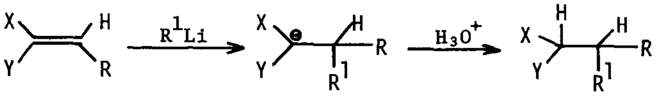
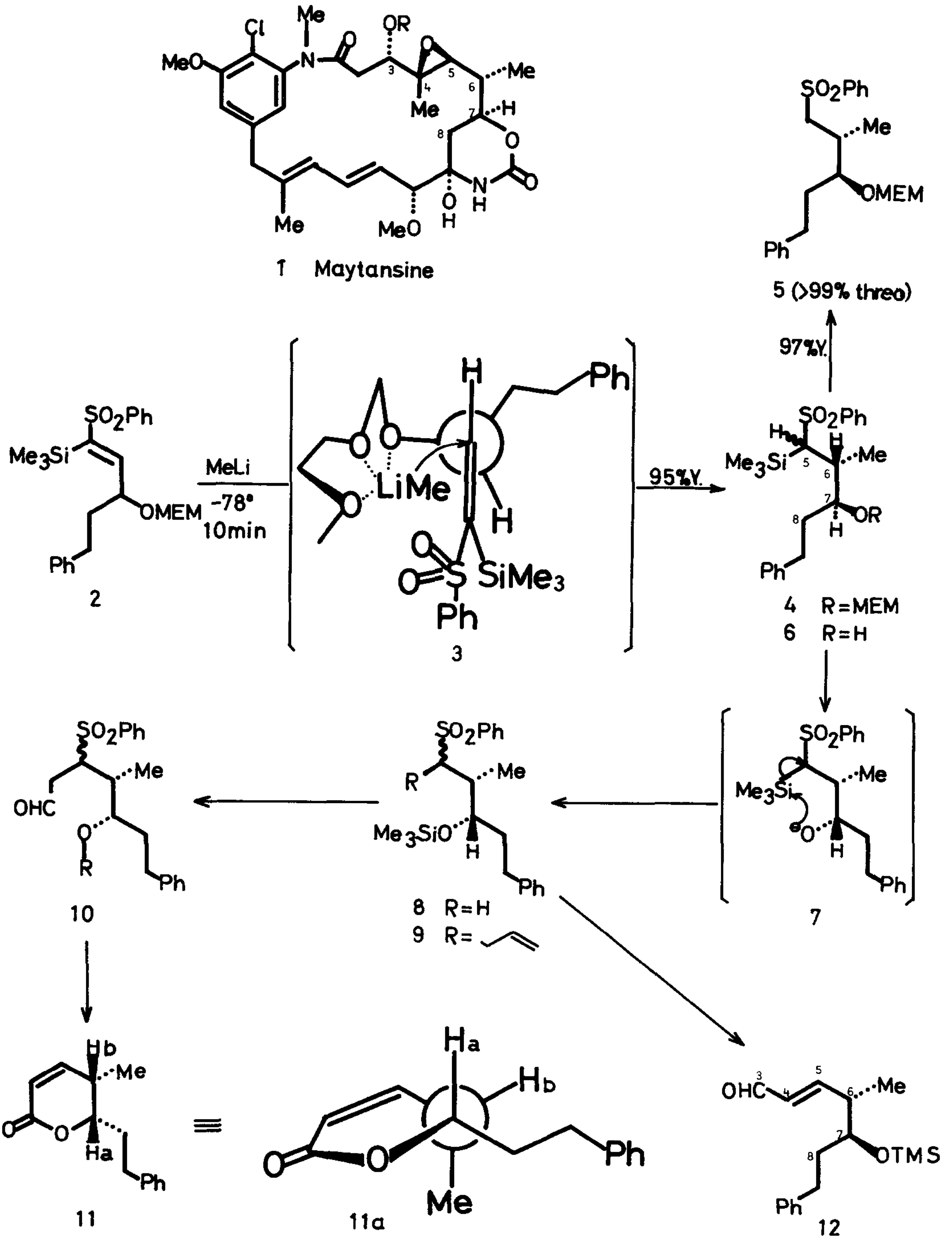
Summary: Acyclic asymmetric induction was achieved in >99 % threo formation via coordinated intermediate (3) in the heteroconjugate addition (2 to 4); the heteroatom in the adduct being used for elongation of the carbon chain toward maytansine (1).

During the course of our synthetic studies directed toward an ansamacrocyclic antitumor agent, maytansine (1),[1] we developed a new reaction in which lithium alkyls could add to the tri-substituted olefins conjugated with heteroatoms (X and Y in eq. 1) such as silicon and sulfur. We propose to term "Heteroconjugate Addition" for this conceptually new type of reaction. Heteroconjugate additions involving second or third row atoms as X & Y, have been explored very recently in only exo-methylene cases (R=H)[2], but it has never been reported on the reaction in tri-substituted hetero-olefins (R=alkyl) which should have high potentiality facilitating synthesis of the macrocyclic natural product. Thus, in the hetero-olefin with asymmetric center in 'R', we developed a remarkable asymmetric induction in the heteroconjugate addition. Here is described its substantiating methodology for the threo-asymmetric induction (corresponding to the carbon 6 and 7 of 1) and for elongation of carbon chain toward 1 using these heteroatoms efficiently.



[eq. 1]

The substituted olefin (2), in which the double bond conjugated with both sulfur and silicon atoms and carries methoxyethoxymeth(MEM)oxy group in its allylic position, was prepared in two steps from 2-MEM-oxy-4-phenylbutanal by treatment with lithium bis-(trimethylsilyl)-phenylsulfinylmethylide.[3] This hetero-olefin (2), being a regiomixture (E/Z = 1/4), was treated with methyl lithium in THF at -78 °C for 10 min to afford 4 in 95 % yield.[4] When TMS in 4 was taken off with KF-MeOH, the product 5 (in 97 % yield) was a single[5] 'threo'-compound, the stereostructure of which was proven by leading into a cyclic compound (11, *vide infra*). Thus, the


1 Maytansine
2
MeLi
-78°
10min
3
95%Y.
4 R=MEM
6 R=H
97%Y.
5 (>99% threo)
7
8 R=H
9 R=
10
11
≡
11a
12

stereochemistry between C6 and C7 in 4 was also in threo orientation. In consequence, the heteroconjugate addition of methyl lithium to 2 occurred in >99 % diastereoselectively. The stereochemical control in this addition was intended to proceed *via* a transition intermediate (3), so the methyl anion to attack the beta carbon of the olefin only from one side when one employed a group such as MEM, which strongly coordinated with methyl group through lithium counter cation.[6]

We found that the alcohol 6 [obtained as needles[7] (m.p. 145 °C) from 4 by acid hydrolysis] was quantitatively converted into the silyl ether 8 by treatment with catalytic amount of base (NaH) or KF in THF. This conversion involved exothermic intramolecular transfer of the TMS group from the carbon to hydroxy oxygen atom (see 7), which might dissociate intermolecularly *via* chain mechanism by the sulfone-carbanion formed. Further elongation of the carbon chain was substantiated by use of the carbanion formed by this silicon-transfer. When one treated 6 with 1 eq. of n-BuLi and then with allyl bromide, for instance, the alkylated product 9 could be obtained in quantitative yield. Ozonolysis of 9, when the ozonide of 9 was treated with triethylamine[8], gave exclusively the trans-α,β-unsaturated aldehyde 12 [δ 9.46(1H, d, J= 7), 6.87 (1H, dd, J= 16 & 7), 6.05(1H, dd, J= 16 & 7)], which could be one of the good synthetic intermediates for 1.

Proof of stereochemistry In order to prove the threo-asymmetric induction by the heteroconjugate addition, the six-membered cyclic compound, 11 was prepared in 4 steps from 9. Ozonolysis of 9, worked up by triphenylphosphine, gave the aldehyde 10 [48 % yield; δ 9.50 ppm, s], which was successively treated with dil. HCl, Jones reagent, and then triethylamine to produce the unsaturated lactone 11 [m/e 216; ν 1740 cm^{-1}] in 62 % overall yield. The 200 MHz pmr spectra of 11 showed that Ha (δ 4.38 ppm) coupled with Hb in 3.5 Hz,[9] and that the two substituents on the butenolactone ring located in cis-orientation, thus threo configuration in C6 and C7 in 4. Further confirmation for the stereochemistry was done by preparing a 1 : 1 mixture of threo and erythro isomer of the alcohol 6 [obtained by oxidation of 6 with Collins reagent and then by reduction with $NaBH_4$[10]], which was converted into the butenolactone mixture (cis/trans = 1/1) corresponding to 11. Pmr of the trans isomer[9] of 11 showed its proton corresponding to Ha at δ 4.02 ppm to couple with Hb in 10.0 Hz.

Further synthetic study to 1 is now in progress with chiral oxy-aldehyde as the starting materials, and the general utility of the series of reactions will be described elsewhere.

REFERENCES AND NOTES

1. S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger and R. F. Bryan, J. Am. Chem. Soc., 94, 1354 (1972); S. M. Kupchan et al., J. Org. Chem., 42, 2349 (1977).
2. Heteroconjugate addition involving Si, Se and/or S (as X, Y in eq. 1) by lithium alkyls in exo-methylene case (R=H); see, B-Th. Gröbel and D. Seebach, Angew. Chem. Int. Ed., 13, 83 (1974); N. H. Andersen et al., Tetra. Lett., 4315 (1978); S. Raucher and G. A. Koolpe, J. Org. Chem., 43, 4252 (1978). The substituted olefins (R= isopropyl or phenyl) were studied by us, and the results will be presented elsewhere. In case of silicon and sulfone in eq. 1 (R= H) as the heteroatoms, the same reaction was published recently: see, M. van der Leij and B. Zwanenburg, Tetra. Lett., 3383 (1978).
3. B-Th. Gröbel and D. Seebach, Chem. Ber., 110, 852 (1977).
4. Adduct 4 comprized two diastereoisomers at C5 and C6 in the ratio of ca. 13:1 (by cmr), but not the diastereo-mixture at C6 and C7 at all. The regio-isomers of 2 [E (olefinic H; δ ca.7.5 ppm) and Z (δ 6.56 ppm, d, J= 9 Hz)] were separated by silica gel chromatography and then each isomer was treated with methyl lithium to give the adducts 4 (96% and 95% yield, respectively) which were superimposable to each other in the pmr, cmr and tlc.
5. determined by cmr: 5 ($CDCl_3$) δ 15.2(q), 31.4(t), 32.3(2C; d & t), 58.5(t), 58.9(q), 67.4(t), 71.7(t), 80.0(d), 94.8(t), 125.9(d), 127.9(2C), 128.2(2C), 128.4(2C), 129.2(2C), 133.4(d), 140.1(s), 141.5(s) ppm.
6. Coordination of lithium cation with oxygen atoms in polyether has been reported: e.g., A. I. Mayers, G. S. Poindexter and Z. Brich, J. Org. Chem., 43, 892 (1978).
7. Analysis: found C 64.43, H 7.83; $C_{21}H_{30}O_3S_1Si_1$requires, C 64.57, H 7.74 %.
8. For reactivity of triethylamine to cleave ozonides: see, M. Isobe et al., Tetra. Lett., 703 (1977) and H. Iio et al., Tetrahedron, 34, 941 (1979).
9. The coupling constants of Ha of 14 were measured in 200, 100 and 60 MHz to give [9.40, 4.15, 3.54], [9.12, 4.44, 3.48] and [8.6, 5.2, 3.6] Hz's, respectively. Sets of underlined numerals, the sum being constant (ca. 13.6), are apparent J's between Ha and the neighbouring methylene protons on the side chain, indicating higher order complication. Constant number (ca. 3.5) is the true coupling constant between Ha and Hb, which was confirmed by spin decoupling in 200 MHz. However, these numbers corresponding to the trans isomer of 11 were [10, 6.5, 5.7] in all cases of the three different magnetic strength. Spin decoupling study was done with JEOL FX-200 instrument by Mr. M. Ohuchi of JEOL company and 60 MHz measurement was done by Prof. H. Nakata of Aichi Kyoiku College; to whom cordial thanks are due.
10. The ratio of the two isomers was 1:1 or 3:2 by the reduction with DIBAL-H or L-Selectride, respectively. None or little asymmetric induction was observed in these reduction with bulky hydride reagents. The ratios were determined from the intensity of methyl signals of threo (δ 1.02 ppm, d, J= 7.0 Hz) and erythro (δ 1.12 ppm, d, J= 6.7 Hz) isomer.

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