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Efficient Synthesis of a Carbocyclic Core Moiety with the Stereochemistry of the C-1027 Chromophore

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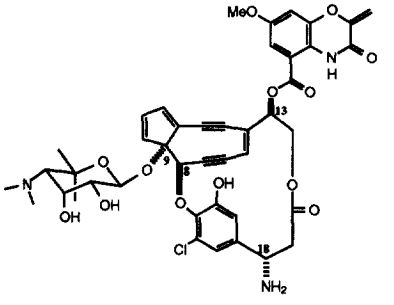
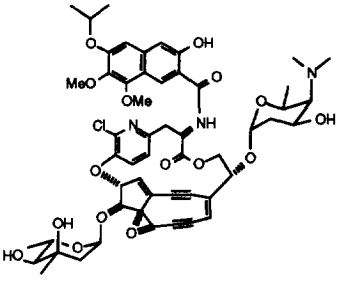
Abstract: A stereoselective and concise route to the bicyclo[7.3.0]dodecadiyne core moiety (**26**) of the C-1027 chromophore (**1**) through highly efficient $LiN(TMS)_2/CeCl_3$-mediated cyclization of alkynyl aldehyde **24** has been established. Copyright © 1996 Elsevier Science Ltd

We recently reported the efficient cyclization of the conformationally non-rigid precursor **3** to the highly strained nine-membered cyclic diyne **4**, a model compound for the C-1027 chromophore (**1**),[1] using $LiN(TMS)_2/ CeCl_3$.[2,3] However, the reaction of diastereomer **5** gave **6** as a mixture of stereoisomers in low yield (Scheme 1).[2] Very recently, the configuration of the C-1027 chromophore (**1**) has been determined, as shown below.[4] Therefore, it would be useful in synthetic studies of **1** and related molecules such as kedarcidin (**2**)[5] to know whether the yield and stereoselectivity of the intramolecular acetylide additions of diastereomers **7** and **9** are affected by the relative configurations of C4, C9 and C13.

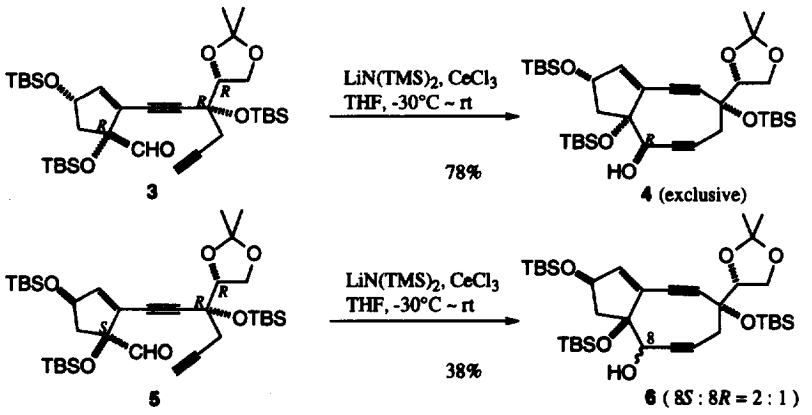


C-1027 chromophore (1)

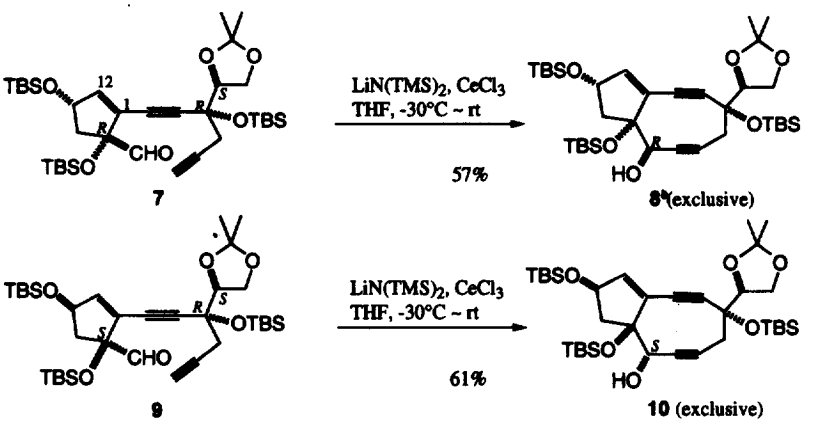


Kedarcidin chromophore (2)

Our results are shown in Scheme 2. Both **7** and **9** cyclized in better yield than **5** and in a highly diastereoselective manner. Thus, only diastereomer **5** was not an appropriate substrate for this cyclization reaction. Diastereomer **8**, which possesses the same stereochemistry as **1**,[4b] has been synthesized effectively from **7**. However, **7** had been prepared from minor product **13** of Grignard addition[6] (Scheme 3), and the C12-C1 double bond was constructed by shifting from the C11-C12 position.[2] Therefore, we developed a stereoselective route to an intermediate corresponding to **13**. After considerable preliminary experiments,[7] we found that acyclic fragment **18** was the most suitable for obtaining the desired stereoisomer selectively through 1,2-chelation control in the addition reaction of the propargyl Grignard reagent (Scheme 4). Ketone **18** was

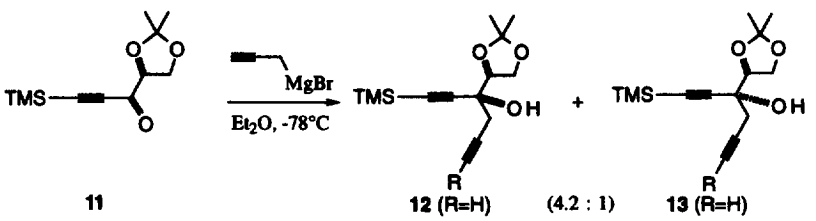


Scheme 1. Differences in efficiency and stereoselectivity between the intramolecular acetylide additions of diastereomers **3** and **5**.[2]



Scheme 2. The efficient intramolecular acetylide addition reactions of diastereomers **7** and **9**.

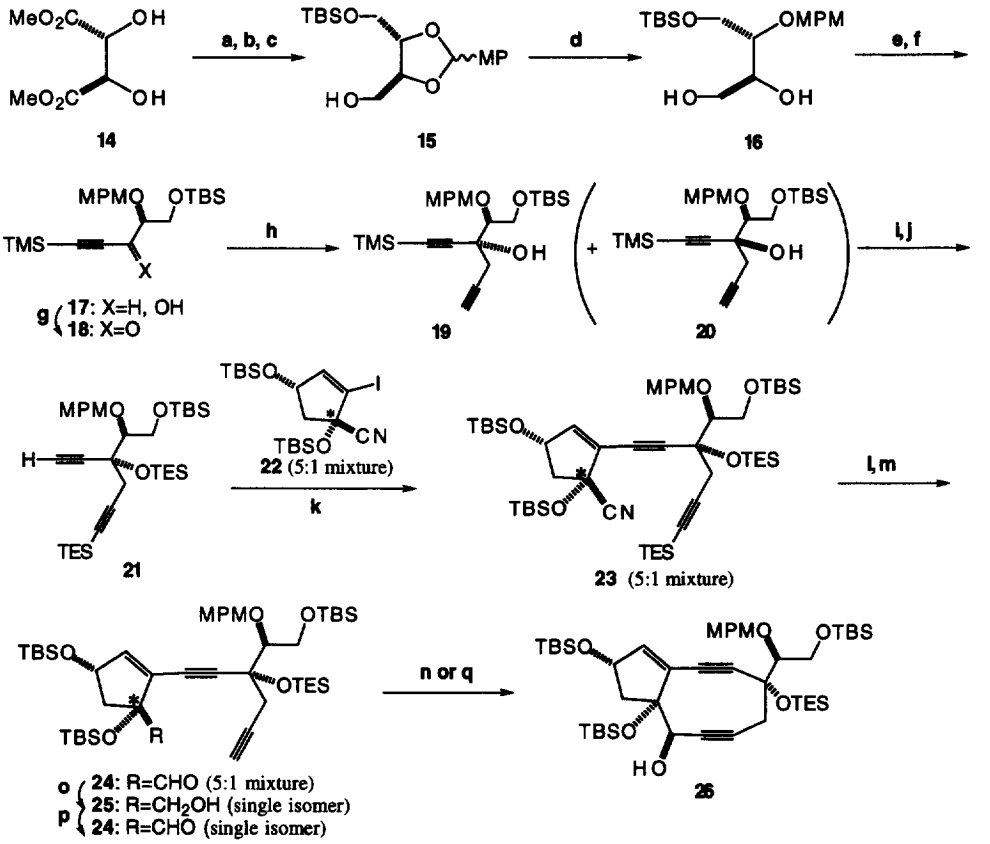
synthesized from *L*-(+)-dimethyl tartrate **14**. While the reaction of **18** with the propargyl Grignard reagent in an ether solvent always gave a 1:1 mixture of **19**[8] and **20**, regardless of the presence or absence of $MgBr_2 \cdot OEt_2$, stereoselectivity was improved to 2.5:1 in CH_2Cl_2/Et_2O (4:1).[9] In the presence of $ZnBr_2$ (3.9 eq), high stereoselectivity favoring **19** (13:1) was achieved.[10] Cyclopentene derivative **22**[11,12] was designed as a segment to couple with alkyne **21**. This coupling was conducted under standard Hagihara-Sonogashira conditions[13] to give **23**. The TES group on the alkyne carbon of **23** was removed selectively,[14] and the nitrile



Scheme 3. Addition reaction of the propargyl Grignard reagent to ketone **11**.

group was then reduced to aldehyde **24**, still as a diastereomeric mixture. Treatment of **24** with $LiN(TMS)_2$/$CeCl_3$ gave the desired nine-membered diyne **26**[15] (55% yield), which is stable at room temperature for a few days.[2] To clarify the efficiency of this cyclization, pure **24** was prepared through reduction-separation-oxidation sequence. The cyclization of pure **24** afforded **26** as a single isomer in 84% yield. Thus, **24** showed very high efficiency in the cyclization. On the other hand, **5** which gave low efficiency in the cyclization exhibited NOE (3.1%) between an acetonide methyl and C12 vinyl proton. These observations suggest that there would exist unfavorable steric interactions between the acetonide group and the cyclopentene moiety in the transition state for the cyclization of **5**.

In summary, we have confirmed that the $LiN(TMS)_2/CeCl_3$-mediated intramolecular acetylide addition to aldehyde is a general method for constructing a highly strained nine-membered diyne system[2,16] and have established a stereoselective and concise route to the key intermediate (**26**) for the total synthesis of the C-1027 chromophore (**1**).



Scheme 4. *Reagents and conditions*: (a) *p*-$MeOPhCH(OMe)_2$, cat. TsOH, 100°C. (b) $LiAlH_4$, THF, 0°C, 82% (2 steps). (c) NaH, THF, 0°C, then TBSCl, 100%. (d) $LiAlH_4$, $AlCl_3$, Et_2O, -50°C, 80%. (e) $NaIO_4$, 60% aq. THF. (f) Ethynyltrimethylsilane, BuLi, THF, -78°C, 81% (2 steps). (g) Dess-Martin periodinane, CH_2Cl_2. (h) $HCCCH_2MgBr$, $ZnBr_2$, CH_2Cl_2/Et_2O (2:1), 82% (2 steps) (**19**:**20**=13:1). (i) BuLi, THF, -70°C, then TESCl, 74%. (j) Bu_4NBr, THF, 1M aq. NaOH, 73%. (k) **22**, cat. $PdCl_2(PPh_3)_2$, cat. CuI, Et_2NH, 50°C, 47% from **22**. (l) $AgNO_3$, THF, *i*-PrOH, H_2O, then 2,6-lutidine, 59%. (m) DIBAL, CH_2Cl_2, -50°C, 74%. (n) $LiN(TMS)_2$, $CeCl_3$, THF, -30°C to r.t., 55% for a 5:1 diastereomeric mixture of **24**. (o) DIBAL, CH_2Cl_2, -50°C and separated from an isomer, 59%. (p) Dess-Martin periodinane, 83%. (q) $LiN(TMS)_2$, $CeCl_3$, THF, -30°C to r.t., 84% for pure **24**.

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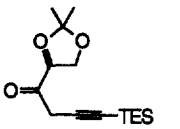
7. For instance, addition reactions of lithium or magnesium trimethylsilylacetylide to **27** in the presence of $CeCl_3$ gave **13** (R=TES) as a major product in ratios of 1.5:1 and 2.5:1, respectively.[6] The reaction did not occur without $CeCl_3$.



27

8. **19**: colorless oil; $[\alpha]_D^{30}$ +12 (c 1.24, $CHCl_3$); IR (neat) ν 3464, 3314, 2958, 2862, 2172, 1613, 1589, 1516, 1303, 1251 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ 0.10 (6H, s), 0.20 (9H, s), 0.95 (9H, s), 2.04 (1H, dd, J=2.5, 2.5Hz), 2.65 (1H, dd, J=16.5, 2.5Hz), 2.79 (1H, dd, J=16.5, 2.5Hz), 3.68 (1H, dd, J=4.1, 3.0Hz), 3.80 (3H, s), 4.03 (1H, dd, J=10.7, 3.0Hz), 4.25 (1H, dd, J=10.7, 4.1Hz), 4.25 (1H, s), 4.61 (1H, d, J=11.0Hz), 4.76 (1H, d, J=11.0Hz), 6.88 (2H, AA'BB'), 7.30 (2H, AA'BB'); Anal. Calcd. for $C_{25}H_{40}O_4Si_2$: C, 65.17; H, 8.75. Found: C, 64.98; H, 8.50.
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15. **26**: pale yellow oil; $[\alpha]_D^{23}$ -57 (c 0.48, CH_2Cl_2); IR (neat) ν 3452(br), 2958, 2934, 2886, 2860, 2860, 1615, 1516, 1473 cm^{-1}; ^1H NMR (600MHz, CD_2Cl_2) δ 0.08 (3H, s, TBS), 0.09 (6H, s, TBS), 0.09 (3H, s, TBS), 0.15 (3H, s, TBS), 0.15 (3H, s, TBS), 0.70 (6H, q, J=8.0Hz, TES), 0.89 (9H, s, TBS), 0.89 (9H, s, TBS), 0.92 (9H, s, TBS), 0.94 (9H, t, J=8.0Hz, TES), 1.40 (1H, d, J=8.6Hz, C^8-OH), 1.87 (1H, dd, J=13.8, 4.2Hz, H^{10}), 2.29 (1H, dd, J=16.5, 1.2Hz, H^5), 2.73 (1H, dd, J=13.8, 7.8Hz, H^{10}), 2.89 (1H, d, J=16.5Hz, H^5), 3.54 (1H, dd, J=7.9, 2.0Hz, H^{13}), 3.77 (3H, s, MPM), 3.84 (1H, dd, J=10.9, 7.9Hz, H^{14}), 3.97 (1H, br d, J=8.6Hz, H^8), 4.21 (1H, dd, J=10.9, 2.0Hz, H^{14}), 4.57 (1H, d, J=10.8Hz, MPM), 4.72 (1H, ddd, J=7.8, 4.2, 2.3Hz, H^{11}), 4.80 (1H, d, J=10.8Hz, MPM), 6.09 (1H, d, J=2.3Hz, H^{12}) 6.84 (2H, AA'XX', MPM), 7.27 (2H, AA'XX', MPM); ^{13}C NMR (150MHz, CD_2Cl_2) ppm -4.8, -4.7, -4.2, -4.2, 6.5, 7.5, 14.7, 18.7, 18.9, 19.0, 26.4, 26.4, 26.6, 33.0 (C^5), 47.4 (C^{10}), 56.0, 66.4 (C^{14}), 69.6 (C^8), 74.5 (C^{11}), 75.2, 80.4 (C^4), 86.4 (C^{13}), 89.8 (C^3 or C^6), 91.7 (C^7), 92.1 (C^2), 92.7 (C^9), 98.8 (C^3 or C^6), 114.4, 129.1 (C^1), 130.5, 131.8, 142.8 (C^{12}), 160.0.
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