Pergamon

Tetrahedron Letters 43 (2002) 2815–2818

TETRAHEDRON LETTERS

Stereoselectivity in the intramolecular Nozaki–Hiyama–Kishi reaction: influence of the substitution pattern and protecting groups in the construction of 10-membered lactones

Ronaldo A. Pilli* and Mauricio M. Victor

Instituto de Química, UNICAMP, CP 6154, Campinas 13083-970, Brazil

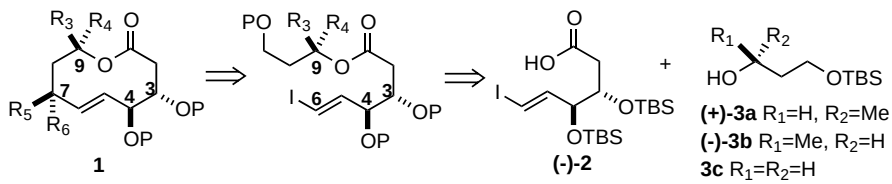
Received 8 November 2001; revised 15 February 2002; accepted 18 February 2002

Abstract—The use of the intramolecular Nozaki–Hiyama–Kishi reaction to construct 10-membered lactones is described. The influence of the nature of the protecting groups at C3 and C4 and the presence of the methyl group at C9 on the stereochemistry of the newly formed stereogenic center at C7 was investigated. Matched induction led to the preparation of the decanolide moiety with high degree of stereoselection. © 2002 Elsevier Science Ltd. All rights reserved.

Decanolides have attracted special attention over the last years.[1] An important family of compounds are the decarestrictines,[2] mainly decarestrictine D due to its ability as an inhibitor of cholesterol biosynthesis and DNA-binding activity.[3] Such significant biological properties contributed to the interest in devising synthetic approaches to this family of natural products. The synthetic approach to lactones has traditionally focused mainly on the use of fragmentation/ring expansion reactions and on lactonization strategies in order to build the lactone ring.[4] Recently, examples of the construction of lactones through the formation of the C–C bond appeared[5] and the intramolecular Nozaki–Hiyama–Kishi (NHK) coupling reaction[6] stands as a promising protocol. The influence of the protecting groups in the stereochemical outcome of the NHK reactions has been reported previously.[7] During our studies on the total synthesis of decarestrictine D, we observed loss of stereochemical control at C7 upon changing the OTBS groups at C3 and C4 in (−)-**4a** for the isopropylidene acetal group.[5d] These observations prompted us to expand our study on the influence of the conformational bias of the acyclic precursor in the stereochemical course of the reaction.

According to our approach, the construction of the decanolide ring **1** would arise from the formation of the C6–C7 bond (Scheme 1). The acyclic precursors would be prepared from the condensation of acid (−)-**2**[8] and alcohols **3a**–**c**. The change of the protecting groups at C3 and C4 would arise from manipulation of the protecting groups at these oxygenated positions in the acyclic precursors. Our expectation to control the stereogenic center to be created at C7 was based on the interplay of transannular interactions and on the proposal by Overman and coworkers of a well organized arrangement in the transition state of the NHK reaction. During the synthesis of (−)-deacetoxyalcionine,[9] these authors proposed the chelation of the vinylic chromium species to the carbonyl group of the aldehyde in order to explain the outstanding diastereoselectivity observed in the formation of the 9-membered ring (>20:1). As applied to our case, we would expect that:

(i) the methyl group at C9 would adopt a pseudo-equatorial orientation in the transition state thus



Scheme 1.

* Corresponding author. E-mail: pilli@iqm.unicamp.br

PII: S0040-4039(02)00347-7

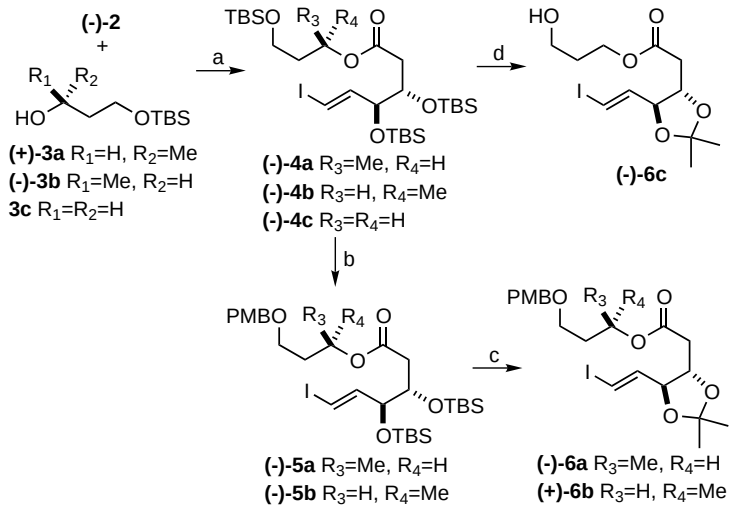
determining the relative position of the C9–C7 moiety and influencing carbonyl face-selection, assuming that a chair–chair–chair conformation would prevail;

(ii) the judicious choice of the protecting group at C3 and C4 could dictate the relative positioning of the C5–C6 and C2–O–C7 fragments: OTBS groups which are bound to adopt *anti* relative orientation would enforce *gauche* orientation of the C2–C3/C4–C5 bonds while the cyclic isopropylideneacetal as protecting group would keep the side chains apart.

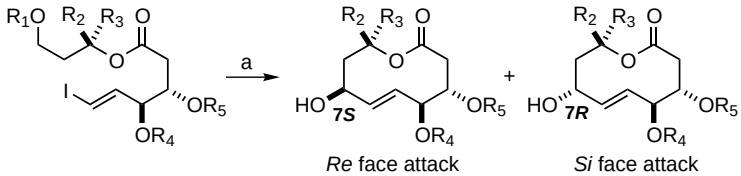
The synthesis of the acyclic precursors began with the coupling of acid (−)-**2** with alcohols **3a**–**c** employing the Yamaguchi protocol, which furnished the TBS-protecting acyclic precursors **4a**–**c** in 64–83% yield (Scheme 2). In order to prepare the isopropylideneacetal-protected precursors, different strategies were employed. The C9-methyl substituted esters (−)-**4a** and (−)-**4b** required[10] changing the primary hydroxyl protecting group from TBS to PMB, and after removal of the secondary TBS groups of (−)-**5a** and (−)-**5b** with HF·pyridine complex, the diols obtained were treated with 2,2-dimethoxypropane and PPTS in DMF to give (−)-**6a** and (+)-**6b** in 63 and 40% overall yield, respectively. The C9 unsubstituted (−)-**6c** was obtained directly from (−)-**4c** after removal of TBS-groups with a large excess of HF·pyridine complex and treatment with 2,2-dimethoxypropane and PPTS in CH_2Cl_2, in 78% overall yield.

At this point we were ready to apply the intramolecular NHK reaction to the aldehydes derived from **4a**–**c** and **6a**–**c**. The primary TBS groups in compounds **4a**–**c** were selectively removed and oxidized to the corresponding aldehydes with Dess–Martin periodinane, while the PMB-group in **6a**–**b** was removed by treatment with DDQ and the corresponding alcohols were oxidized as already described. Alcohol (−)-**6c** was oxidized with Dess–Martin periodinane (Scheme 3). All the aldehydes obtained were not purified but immediately used in the NHK coupling step. The coupling required 15 equiv. of $CrCl_2$ (containing 0.5% of $NiCl_2$) in degassed DMF at high dilution and at room temperature. The results are described below (Table 1).

The assignment of the stereochemistry at C7 was achieved by ^{1}H NMR as described for (−)-**7a**: H7 appeared as a triplet of doublets at δ 4.21 with two large coupling constants (10.8 and 8.4 Hz, *trans*-diaxial orientation for H6 and $H8_{ax}$) and a small one (3.4 Hz, $H8_{eq}$), suggesting a chair–chair–chair conformation (Fig. 1). Such an assignment was supported by nOe experiments: 4.3% increment at H7 was observed upon irradiation of H9 and eventually by its conversion to (−)-decarestrictine D.[5a,5d] Accordingly, the ^{1}H NMR spectra of (−)-**11b** displayed H7 as a triplet of doublets



Scheme 2. Key: (a) (i) (−)-**2**, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF. (ii) **3**, benzene, DMAP [(−)-**4a** 83%, (−)-**4b** 64%, (−)-**4c** 74%]. (b) (i) HF·pyridine, pyridine, THF. (ii) PMB–trichloroacetimidate, Et_2O, TfOH (cat) [(−)-**5a** 74%, (−)-**5b** 53%, two steps]. (c) (i) HF·pyridine, pyridine, THF. (ii) 2,2-Dimethoxypropane, PPTS, DMF [(−)-**6a** 85%, (+)-**6b** 75%, two steps]. (d) (i) HF·pyridine, pyridine, THF. (ii) 2,2-Dimethoxypropane, PPTS, CH_2Cl_2 (78%, two steps).



Scheme 3. Key: (a) (i) R_1 deprotection (except for (−)-**6c**). (ii) Dess–Martin oxidation. (iii) NHK cyclization. For yields, see Table 1.

Table 1. Diastereoselectivity in the NHK cyclization (see Scheme 3)

Entry	Precursor	R_1	R_2	R_3	R_4	R_5	Yield (%)[a]	Compound	Ratio 7*S*/7*R*[c]
1	(−)-**4a**	TBS	Me	H	TBS	TBS	31	**7a**/**7b**	>97:3
2	(−)-**4b**	TBS	H	Me	TBS	TBS	32	**8a**/**8b**	1:2
3	(−)-**4c**	TBS	H	H	TBS	TBS	27	**9a**/**9b**	1.3:1
4	(−)-**6a**	PMB	Me	H	$-C(Me)_2-$		29	**10a**/**10b**[d]	1:2
5	(+)-**6b**	PMB	H	Me	$-C(Me)_2-$		44	**11a**/**11b**	1:22
6	(−)-**6c**	H	H	H	$-C(Me)_2-$		59[b]	**12a**/**12b**	1:3.3

[a] Overall yield, three steps.
[b] Overall yield, two steps.
[c] Determined by ^1H NMR.
[d] Not separable by column chromatography.

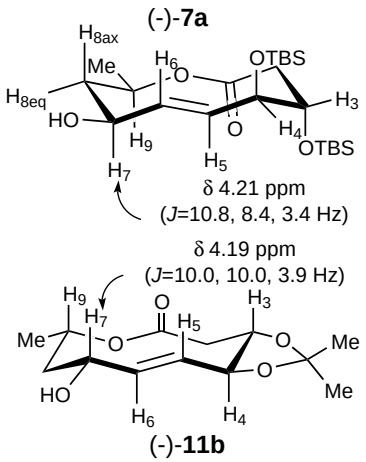


Figure 1.

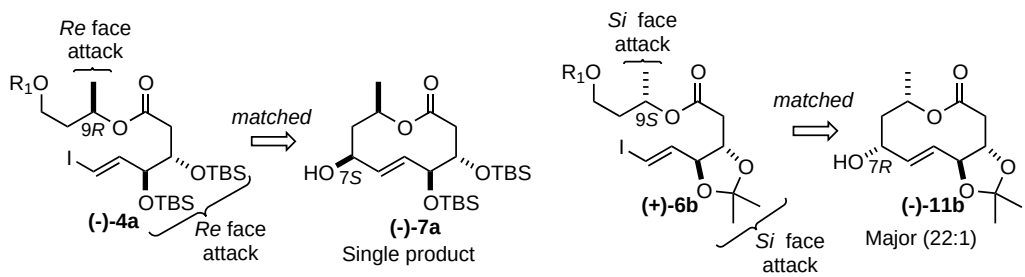
at δ 4.19 (10.0, 10.0 and 3.9 Hz) and 1.7% nOe increment upon irradiation of H9.[11]

When the NHK cyclization was carried out on the TBS-protected esters without substitution at C9 ((−)-**4c**, entry 3), a slight preference for the *Re* face attack was observed. The isopropylidene acetal group at C3/C4 positions steered the addition to the *Si* face albeit with moderate preference (entry 6, Table 1). These results suggest that the judicious choice of the protecting group can determine and influence the carbonyl facial selection. Moreover, the presence of a methyl substitution at C9 also plays an important role in the carbonyl facial selection. A methyl group at C9 with *R* configuration enforces the *Re* face attack as indicated when one compares the results for (−)-**4a** (entry 1) and (−)-**4c** (entry 3) and for (−)-**6a** (entry 4) and (−)-**6c** (entry 6). Meanwhile, the bias for *Si* face addition in the 9*S* methyl substituted substrate is evident upon comparison of the results observed for the NHK cyclization of (−)-**4a** (entry 1) and (−)-**4b** (entry 2) and for the cyclization of (−)-**6a** (entry 4) and (+)-**6b** (entry 5). It is reasonable to describe the combined influence of a 9*R* methyl group and of TBS protecting group at C3 and C4, as well as that of a 9*S* methyl group and an isopropylidene acetal at C3 and C4 as matched cases. These results imply that the construction of the decanolide skeleton can be achieved with high degree of diastereoselection either to afford the (7*S*,9*R*) or (7*R*,9*S*) configuration (Scheme 4).

In conclusion, some key factors that control the stereochemistry of NHK cyclization in the construction of decanolides were investigated. The proper choice of protecting group associated with the correct stereochemistry at C9 allowed the construction of decanolide moiety with high degree of diastereoselection. Further studies are underway.

Acknowledgements

This work was supported by grants from CNPq (Brazil), Volkswagen Stiftung (Germany) and International Foundation for Science (Sweden).



Scheme 4.

References

1. For recent reviews see: (a) Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365–375; (b) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377–1395.
2. (a) Grabley, S.; Granzer, E.; Hütter, K.; Ludwig, D.; Mayer, M.; Thiericke, R.; Till, G.; Wink, J.; Phillips, S.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 56–65; (b) Göhrt, A.; Zeeck, A.; Hütter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 66–73; (c) Grabley, S.; Hamann, P.; Hütter, K.; Kirsch, R.; Kluge, H.; Mayer, M.; Thiericke, R.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 1176–1181; (d) Ayer, W. A.; Sun, M.; Browne, L. M.; Brinen, L. S.; Clardy, J. *J. Nat. Prod.* **1992**, *55*, 649–653.
3. Dräger, D.; Garming, A.; Maul, C.; Noltemeyer, M.; Thiericke, R.; Zerlin, M.; Kirschning, A. *Chem. Eur. J.* **1998**, *4*, 1324–1333.
4. Rousseau, G. *Tetrahedron* **1995**, *21*, 2777–2849.
5. (a) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421–4424; (b) Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O.; de Meijere, A. *J. Org. Chem.* **1998**, *63*, 7811–7819; (c) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 1157–1160; (d) Pilli, R. A.; Victor, M. M. *J. Braz. Chem. Soc.* **2001**, *12*, 373–385.
6. For recent reviews see: (a) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36; (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. C. *Chem. Soc. Rev.* **1999**, *28*, 169–177; (c) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045.
7. For other examples see: (a) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909–4912; (b) Rowley, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735–2737; (c) Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198–5200.
8. For experimental details on the preparation of carboxylic acid **2** from 1,3-propanediol, see Ref. 5d. See also, Ref. 5a.
9. MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392.
10. Free-primary hydroxyl group led to extensive O-C7 to O-C9 migration.
11. For analytical data of compounds (−)-**7a** and **10a**/**10b**, see Ref. 5d; (−)-**11b**: $[\alpha]_{546}$ −9.1 (*c* 0.55, $CHCl_3$); IR (film) 3440, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (dd, $J=15.5$, 9.6 Hz, 1H), 5.47 (dd, $J=15.5$, 9.4 Hz, 1H), 4.97 (dqd, $J=11.2$, 6.5, 1.6 Hz, 1H), 4.19 (td, $J=10.0$, 3.9 Hz, 1H), 4.02 (t, $J=8.9$ Hz, 1H), 3.76 (ddd, $J=11.2$, 8.6, 2.7 Hz, 1H), 2.79 (dd, $J=11.5$, 2.7 Hz, 1H), 2.39 (t, $J=11.4$ Hz, 1H), 1.94 (ddd, $J=14.2$, 4.0, 1.6 Hz, 1H), 1.82 (dt, $J=14.2$, 10.8 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.26 (d, $J=6.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 141.2, 124.3, 109.4, 83.9, 78.1, 71.4, 69.3, 42.5, 37.0, 26.9, 26.8, 21.4.; MS (EI): *m*/*z* 43 (100%), 241 (2%, $[M-CH_3]^+$); HRMS (EI): *m*/*z* Anal. Calcd $C_{12}H_{17}O_5$ $[M-CH_3]^+$ 241.10759; Found 241.10760.