Pergamon

Tetrahedron Letters 42 (2001) 1631–1633

TETRAHEDRON LETTERS

A stereocontrolled approach to substituted piperidones and piperidines: flavopiridol D-ring analogs

Alexandre Gross, David R. Borcherding, Dirk Friedrich and Jeffrey S. Sabol*

Aventis Pharmaceuticals Inc., Route 202-206, PO Box 6800, Bridgewater, NJ 08807-0800, USA

Received 13 November 2000; accepted 1 December 2000

Abstract—A stereocontrolled approach to substituted piperidones and piperidines is presented, and their utility as intermediates for the synthesis of flavopiridol D-ring analogs is described.

Cyclin-dependent kinases (CDKs) belong to a class of enzymes that control the ability of a cell to enter into and proceed through the cell division cycle. These kinases are regulated by cyclin activators and endogenous CDK inhibitors. The loss of this regulation can result in proliferative disorders such as those found in cancers, which make the CDKs attractive therapeutic targets.[1] Flavopiridol (Fig. 1) is a synthetic flavone currently in phase II clinical trials as an anticancer agent whose mechanism of action is believed to be through the inhibition of CDKs.[2] We were interested in preparing flavopiridol D-ring analogs for SAR studies while maintaining the necessary *cis* relationship between the 3-hydroxyl and 4-flavone substituents. We wish to communicate an approach which allows us to stereoselectively prepare substituted piperidones and piperidines, leading to the synthesis of flavopiridol D-ring analogs.

The synthesis (Scheme 1) commences with the Wadsworth–Emmons olefination of aldehyde **1** with trimethyl phosphonoacetate followed by reduction of the resulting α,β-unsaturated ester with diisobutylaluminum hydride (DIBAL) to afford allylic alcohol **2a**. Similarly, olefination of **1** with the anion of dimethyl (2-oxopropyl)phosphonate and reduction of the unsaturated ester with lithium triethylborohydride afforded allylic alcohol **2b**. Johnson *ortho* ester Claisen rearrangement[3] of alcohols **2a** and **2b** provided intermediate γ,δ-unsaturated esters, which were saponified to acids **3a** and **3b**. Stereocontrolled iodocyclization of acids **3a** and **3b** under thermodynamic control as described by Bartlett et al.[4] was completely stereoselective, and the resulting γ-iodolactones were treated with sodium azide to afford multigram quantities of scaffolds **4a** and **4b**. The enolate of γ-azidolactone **4a** was generated using lithium bis(trimethylsilyl)amide (LiHMDS) as the base and treatment with iodomethane afforded the *trans–trans* lactone **5**, whose relative stereochemistry was unambiguously determined from ^{1}H NMR NOESY and NOE difference data.[5] In addition, other electrophiles such as allyl bromide, benzyl bromide, and ethyl bromoacetate also reacted with the enolate of **4a** in a stereocontrolled fashion, and these results will be described elsewhere. Hydrogenation of azide **5** did not produce piperidone **6**, however, treatment of the hydrogenation product with catalytic sodium methoxide in methanol[6] readily afforded piperidone **6** whose relative stereochemistry was assigned from NMR data.[5] The potential of piperidone **6** for further functionalization is being explored. The hydroxyl group of **6** can be protected or manipulated, and the lactam is useful for *N*-alkylation or for the introduction of carbon nucleophiles by *N*-carbamate formation, followed by nucleophilic lactam ring opening and intramolecular reductive amination.

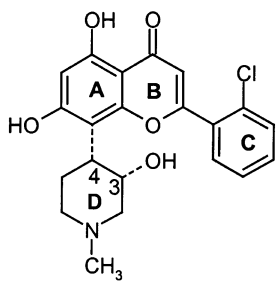
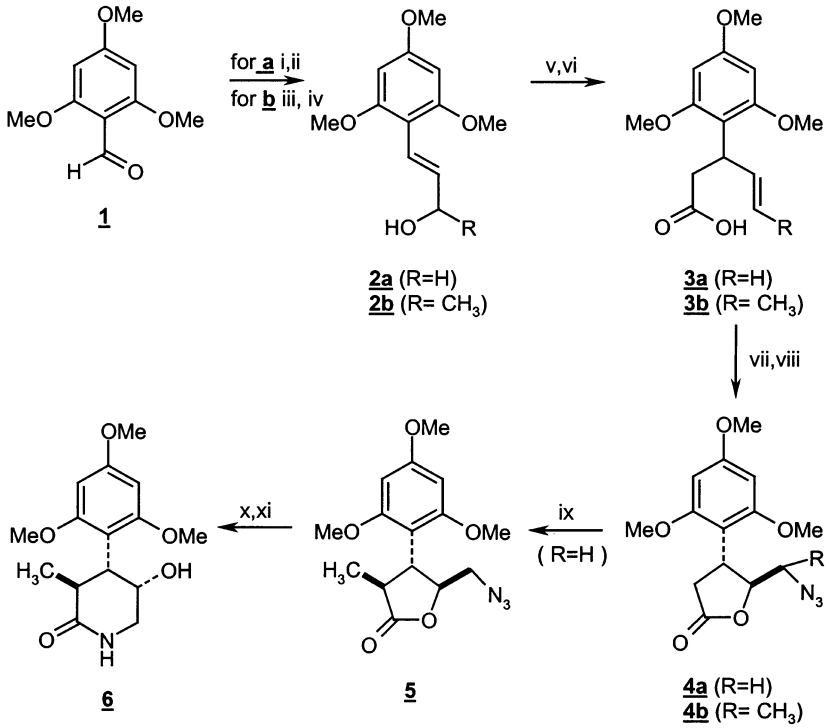


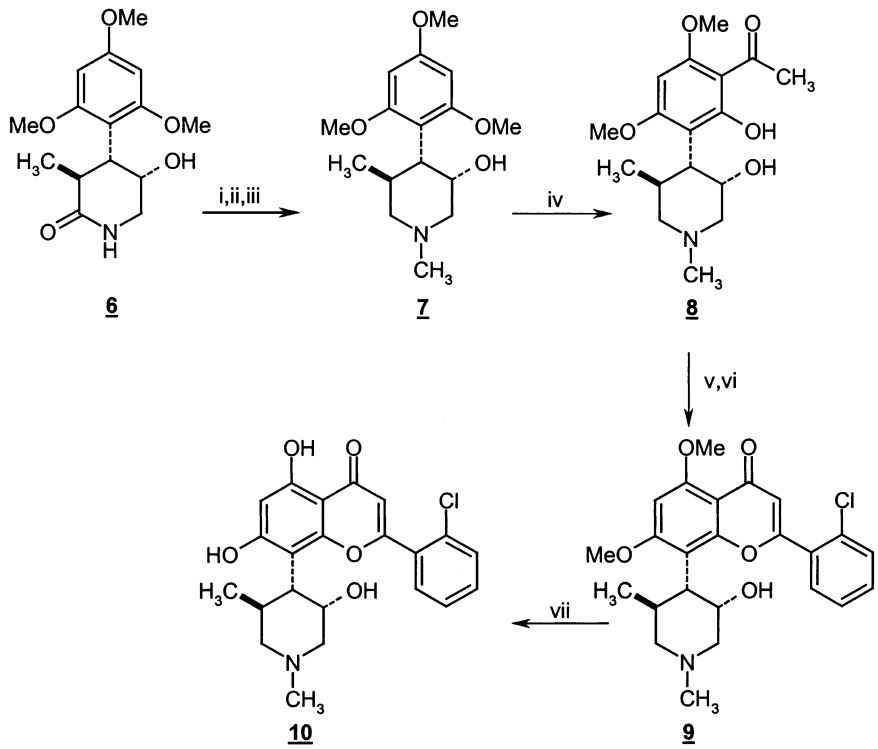
Figure 1. Flavopiridol.

* Corresponding author. Tel.: 1-908-231-3092; fax: 1-908-231-3577; e-mail: jeff.sabol@aventis.com

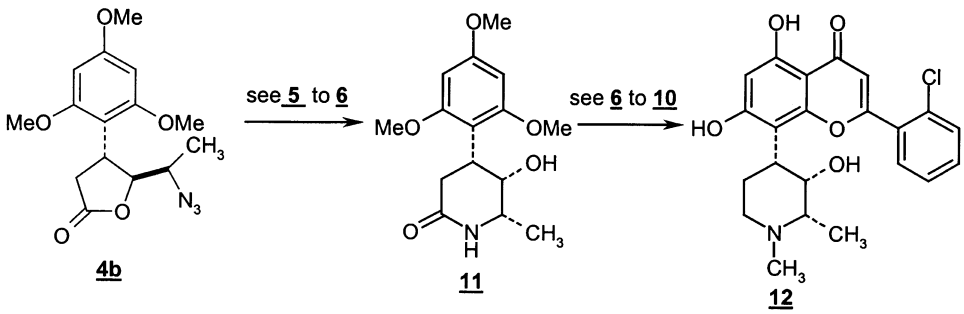
0040-4039/01/$ - see front matter
PII: S0040-4039(00)02350-9



Scheme 1. Conditions: (i) $(CH_3O)_2P(O)CH_2CO_2CH_3$, THF, LiHMDS, 0°C–rt, 90%; (ii) DIBAL, toluene, rt (1 h), 98%; (iii) NaH, dioxane, $(CH_3O)_2P(O)CH_2C(O)CH_3$, 100°C (1 h), 80%; (iv) $LiEt_3BH_3$, THF, 0°C, 95%; (v) $CH_3C(OC_2H_5)_3$, *t*-$BuCO_2H$ (5%), *o*-xylene, 135°C (2 h), **a** = 60%, **b** = 70%; (vi) 1N NaOH, MeOH, 50°C (4 h), **a** = 85%, **b** = 75%; (vii) I_2 (3 equiv.) CH_3CN, 0°C (24 h), **a** = 80%, **b** = 75%; (viii) NaN_3, DMF, 100°C (3 h), **a** = 88%, **b** = 95%; (ix) LiHMDS, THF, −70°C (0.5 h), then CH_3I (−70°C–rt), 60%; (x) H_2 (60 psi), EtOH, 10% Pd/C, quant.; (xi) NaOMe (cat.), MeOH, 65°C (2 h), 75%.



Scheme 2. Conditions: (i) *t*-Butyldimethylsilyl chloride, imidazole, DMAP, DMF, rt, 95%; (ii) LAH, THF, 65°C (3 h), 90%; (iii) aq. CH_2O, $NaBH_3CN$, CH_3CN, pH 5.0, 90%; (iv) Ac_2O, $BF_3{\cdot}OEt_2$, then 10% aq. NaOH, 30°C (6 h), 30–50%; (v) DMF, 95% NaH (5 equiv.), rt (1 h), then methyl 2-chlorobenzoate, rt (16 h), 30%; (vi) 4N HCl/dioxane, rt (16 h); (vii) pyr·HCl, quinoline, 160°C (1 h).



Scheme 3.

The utilization of piperidone **6** in the synthesis (Scheme 2) of a flavopiridol D-ring analog begins with the conversion of **6** to piperidine **7** in 76% yield using a three-step sequence of hydroxyl group protection as a *t*-butyldimethylsilyl ether, lactam reduction with lithium aluminum hydride, and *N*-methylation with concomitant loss of the protecting group. At this point, the published procedure for the synthesis of the flavone portion of flavopiridol was followed.[7] The B-ring annulation was initiated by the conversion of **7** to hydroxyacetophenone **8** via a selective demethylation-Fries rearrangement sequence. Condensation of **8** with methyl 2-chlorobenzoate was followed by cyclodehydration, yielding flavone **9**. Demethylation with pyridinium hydrochloride completed the synthesis of flavopiridol analog **10**.[5] Likewise (Scheme 3), azidolactone **4b** was stereoselectively converted to piperidone **11** in 57% overall yield utilizing the two-step sequence used in the conversion of **5** to **6**. The *cis–cis* relative stereochemistry of **11** was confirmed by NMR.[5] Finally, piperidone **11** was transformed to flavopiridol analog **12**[5] by the same reaction sequence used to convert **6** to **10**.

In conclusion, we have outlined a stereocontrolled approach to useful, substituted piperidones and piperidines, which were further elaborated to flavopiridol D-ring analogs. Additional work and SAR studies will be communicated elsewhere.

References

1. Sielecki, T. M.; Boylan, J. F.; Benfield, P. A.; Trainor, G. L. *J. Med. Chem.* **2000**, *43*, 1–18.
2. Sedlacek, H. H.; Czech, J.; Naik, R.; Kaur, G.; Worland, P.; Losiewicz, M.; Parker, B.; Carlson, B.; Smith, A. *Int. J. Oncol.* **1996**, *9*, 1143–1168.
3. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
4. Gonzalez, F. B.; Bartlett, P. A. *Org. Synth.* **1986**, *64*, 175–181.
5. Selected NMR data: **5** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 s (2H; H-3′/H-5′), 4.80 ddd (J=9.5, 5.5, 3 Hz; H-4α), 3.82 s (3H; 4′-OMe), 3.80 s (6H; 2′-OMe/6′-OMe), 3.69 dd (J=11, 9.5 Hz; H-3β), 3.44 dd (J=13.5, 3 Hz; H-5), 3.33 dd (J=13.5, 5.5 Hz; H-5), 3.32 dq (J=11, 7 Hz; H-2α), significant NOE between H-2α and H-4α. **6** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 s (2H; H-3′/H-5′), 5.86 brs (NH), 4.12 brs (4α-OH), 4.08 brs (H-4β), 3.82 s (9H; 2′-OMe/4′-OMe/6′-OMe), 3.72 dd (J=12, 1.5 Hz; H-3β), 3.50 brdd (J=12.5, 2.5 Hz; H-5β), 3.37 ddd (J=12.5, 3.5, 2.5 Hz; H-5α), 3.33 dq (J=12, 7 Hz; H-2α), 1.04 d (3H; J=7 Hz; H-6), NOEs between axial H-2α and 4α-OH, and between axial H-3β and H-5β. **10** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 dd (J=8, 1.5 Hz; H-6″), 7.54 dd (J=7.5, 2 Hz; H-3″), 7.48 ddd (J=8, 7.5, 2 Hz; H-5″), 7.42 ddd (J=7.5, 7.5, 1.5 Hz; H-4″), 6.40 s (H-3′), 6.30 s (H-7′), 4.15 brs (H-3β), 3.16 dd (J=12, 1 Hz; H-4β), 3.09 brd (J=12 Hz; H-2α), 3.05 brd (J=11.5 Hz; H-6α), 2.85 dddq (J=12, 11, 4, 6.5 Hz; H-5α), 2.46 s (3H; N-CH_3), 2.41 brd (J=12 Hz; H-2β), 1.94 dd (J=11.5, 11 Hz; H-6β), 0.65 d (3H; J=6.5 Hz; H-7). **11** ^{1}H NMR (300 MHz, $CDCl_3$); δ 6.18 s (2H; H-3′/H-5′), 5.72 brs (NH), 4.16 brs (4α-OH), 3.97 ddd (J=13, 6, 1 Hz; H-3β), 3.82 s (6H; 2′-OMe/6′-OMe), 3.81 s (3H; 4′-OMe), 3.80 brs (H-4β), 3.65 brdq (J=2, 6.5 Hz; H-5β), 3.24 dd (J=18, 13 Hz; H-2α), 2.28 dd (J=18, 6 Hz; H-2β), 1.27 d (3H; J=6.5 Hz; H-6), NOEs between axial H-2α and 4α-OH, and between axial H-3β and H-5β. **12** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 ddd (J=7.5, 2, 0.5 Hz; H-3″), 7.56 ddd (J=8, 1.5, 0.5 Hz; H-6″), 7.49 ddd (J=8, 7.5, 2 Hz; H-5″), 7.43 ddd (J=7.5, 7.5, 1.5 Hz; H-4″), 6.42 s (H-3′), 6.31 s (H-7′), 3.85 brs (H-3β), 3.63 ddd (J=13, 4.5, 1.5 Hz; H-4β), 3.08 m (H-6α), 2.58 m (H-5α), 2.45 brq (J=6.5 Hz; H-2β), 2.41 s (3H; N-CH_3), 2.40 m (H-6β), 1.54 m (H-5β), 1.26 d (3H; J=6.5 Hz; H-7), NOEs between axial H-4β and axial H-2β, H-6β.
6. The authors thank Drs. Philip Weintraub and Ronald Bernotas for helpful discussions.
7. (a) Kattige, S. L.; Naik, R. G.; Lakdawalla, A. D.; Dohadwalla, A. N.; Rupp, R. H.; Desouza, N. J. US Patent 4,900,727, 1990; (b) Naik, R.; Lal, B.; Rupp, R. H.; Sedlacek, H. H.; Dickneite, G.; Czech, J. US Patent 5,284, 856, 1988; (c) Naik, R.; Kattige, S. I.; Bhat, S. V.; Alrejy, B.; DeSouza, N. J.; Rupp, R. H. *Tetrahedron* **1988**, *44*, 2081.